Editorials
139 Aromatase inhibitors: what is the true cost? K. E. Houston and D. B. Thomson
140 World Kidney Day 2011: protect your kidneys, save your heart W. G. Driss and M. C. Rialto
Review
144 Assessing individual clinical performance: a primer for physicians I. A. Scott, G. Phelps and C. Brand
Clinical Perspectives
156 Dopamine agonists in the treatment of prolactinoma: are they still first choice? C. M. Ogilvie and S. R. Milson
Original Articles
167 Intraperitoneal distribution imaging in ovarian cancer patients S. J. Danese, R. J. Hicks, V. Johnston, D. Allen, T. Jobling, M. Quine and D. Finlay
172 Randomized cross-over trial comparing inpatient and outpatient administration of high-dose cisplatin K. M. Cox, S. Goel, R. L. O’Connell, M. Boyer, P. J. Beale, R. J. Simes and M. R. Stockler
179 Benchmarking opioids in the last 24 hours of life B. R. Ensor and T. P. Middlemiss
186 Intravenous zoledronic acid and oral alendronate in patients with a low trauma fracture: experience from an osteoporosis clinic S. J. Craig, P. P. Youssef, J. H. Vaile, L. Sullivan and J. F. Bleasel
191 JAK2 mutations in Asian patients with essential thrombocythaemia G-C. Wong, G. L. S. Kam and E. S. C. Koay
Brief Communications
197 Antitopoisomerase antibody positivity predates nailfold capillaroscopy abnormalities in scleroderma. Postulated classification of ‘prescleroderma’ H. Engler, D. Champion, J. C. Wu, J. Guillou, M. McGrath and N. Manolios
199 Atypical clinical presentations of the A3243G mutation, usually associated with MELAS S. Blom, T. Robertson, S. Klengberg, R. D. Henderson and P. McCombe
202 Rituximab-induced serum sickness in refractory immune thrombocytopenic purpura G. Le Guerno, M. Baureid, L. Charras and P. Philippe
Personal Viewpoint
Images in Medicine
210 Beware the glass-eyed patient with liver enlargement A. Nins and M. Varoli
211 Left renal vein thrombosis causing left-sided varicocele S. A. Puthiyaveetil and A. Mathew
Letters to the Editor
Clinical-scientific notes
212 Phaeochromocytoma, neurofibromatosis and gastrointestinal stromal tumour: just a random event? S. E. Sandhu, P. McKenzie, R. Yu and E. Chua
213 Reversal of cardiomyopathy with ivabradine B. Gray, P. MacDonald and D. Kuchar
General correspondence
215 Royal Australasian College of Physicians’ advanced training outside of Australia and New Zealand: trainees’ and supervisors’ perspectives P. Ingram, J. Ha, R. McKinnon, C. Jones and D. Fisher
Brief Communications
202 Antitopoisomerase antibody positivity predates nailfold capillaroscopy abnormalities in scleroderma. Postulated classification of ‘prescleroderma’ H. Engler, D. Champion, J. C. Wu, J. Guillou, M. McGrath and N. Manolios
199 Atypical clinical presentations of the A3243G mutation, usually associated with MELAS S. Blom, T. Robertson, S. Klengberg, R. D. Henderson and P. McCombe
202 Rituximab-induced serum sickness in refractory immune thrombocytopenic purpura G. Le Guerno, M. Baureid, L. Charras and P. Philippe
Personal Viewpoint
Images in Medicine
210 Beware the glass-eyed patient with liver enlargement A. Nins and M. Varoli
211 Left renal vein thrombosis causing left-sided varicocele S. A. Puthiyaveetil and A. Mathew
Letters to the Editor
Clinical-scientific notes
212 Phaeochromocytoma, neurofibromatosis and gastrointestinal stromal tumour: just a random event? S. E. Sandhu, P. McKenzie, R. Yu and E. Chua
213 Reversal of cardiomyopathy with ivabradine B. Gray, P. MacDonald and D. Kuchar
General correspondence
215 Royal Australasian College of Physicians’ advanced training outside of Australia and New Zealand: trainees’ and supervisors’ perspectives P. Ingram, J. Ha, R. McKinnon, C. Jones and D. Fisher

World Kidney Day 2011
Individual clinical performance: a primer for physicians
Prolactinoma: are dopamine agonists still first choice?
Endocrine therapy for breast cancer
Ovarian cancer patients: intraperitoneal chemotherapy
High-dose cisplatin: inpatient and outpatient administration
Editorials
139 Aromatase inhibitors: what is the true cost? K. E. Houston and D. B. Thomson
140 World Kidney Day 2011: protect your kidneys, save your heart W. G. Cooper and M. C. Bixler

Review
144 Assessing individual clinical performance: a primer for physicians I. A. Scott, G. Phelps and C. Brand

Clinical Perspectives
156 Dopamine agonists in the treatment of prolactinoma: are they still first choice? C. M. Ogilvie and S. R. Milson

Original Articles
167 Intraperitoneal distribution imaging in ovarian cancer patients S. J. Dunne, R. J. Hicks, V. Johnston, D. Allen, T. Jobling, M. Quinn and D. Rischin
172 Randomized cross-over trial comparing inpatient and outpatient administration of high-dose cisplatin K. M. Cox, S. Goel, R. L. O’Connell, M. Boyer, P. J. Beale, R. J. Simes and M. R. Stockler
179 Benchmarking opioids in the last 24 hours of life R. R. Simor and T. P. Mikkelsen
186 Intravenous zoleodronic acid and oral alendronate in patients with a low trauma fracture: experience from an osteoporosis clinic S. J. Craig, P. P. Youssef, J. H. Vaile, L. Sullivan and J. F. Bleasel
191 JAK2 mutations in Asian patients with essential thrombocythaemia G. C. Wong, G. L. S. Kam and E. S. C. Koy

Brief Communications
197 Antitopoisomerase antibody positivity predicts nailfold capillaroscopy abnormalities in scleroderma. Postulated classification of ‘prescleroderma’ H. Engler, D. Champion, J. C. Wu, J. Gialluisi, M. McGrath and N. Manolios
199 Atypical clinical presentations of the A3243G mutation, usually associated with MELAS S. Bhom, T. Robertson, S. Klingberg, R. D. Henderson and P. McCombe
202 Rituximab-induced serum sickness in refractory immune thrombocytopenic purpura G. Le Guennou, M. Butard, L. Charras and P. Philippe

Personal Viewpoint

Images in Medicine
210 Beware the glass-eyed patient with liver enlargement A. Niss and M. Vardi
211 Left renal vein thrombosis causing left-sided varicocele S. A. Pathiyaravvei and A. Mathew

Letters to the Editor
212 Phaeochromocytoma, neurofibromatosis and gastrointestinal stromal tumour: just a random event? S. R. Sandhu, P. McKenzie, B. Yu and E. Chua
213 Reversal of cardiomyopathy with ivabradine B. Gray, P. Macdonald and D. Kuchar

General correspondence
215 Royal Australasian College of Physicians’ advanced training outside of Australia and New Zealand: trainees’ and supervisors’ perspectives P. Ingram, J. Ha, B. McMillan, C. Jones and D. Fisher

World Kidney Day 2011
Individual clinical performance: a primer for physicians
Prolactinoma: are dopamine agonists still first choice?
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High-dose cisplatin: inpatient and outpatient administration
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References:
Editorials

139  Aromatase inhibitors: what is the true cost?  
K. E. Houston and D. B. Thomson

140  World Kidney Day 2011: protect your kidneys, save your heart  
W. G. Couser and M. C. Riella

Review

144  Assessing individual clinical performance: a primer for physicians  
I. A. Scott, G. Phelps and C. Brand

Clinical Perspectives

156  Dopamine agonists in the treatment of prolactinoma: are they still first choice?  
C. M. Ogilvie and S. R. Milsom

Original Articles

162  Time and geographical variations in utilization of endocrine therapy for breast cancer in Australia  
A. I. Vitry, L. P. Thai and C. Y. Lu

167  Intraperitoneal distribution imaging in ovarian cancer patients  
S. J. Dawson, R. J. Hicks, V. Johnston, D. Allen, T. Jobling, M. Quinn and D. Rischin

172  Randomized cross-over trial comparing inpatient and outpatient administration of high-dose cisplatin  
K. M. Cox, S. Goel, R. L. O’Connell, M. Boyer, P. J. Beale, R. J. Simes and M. R. Stockler

179  Benchmarking opioids in the last 24 hours of life  
B. R. Ensor and T. P. Middlemiss

186  Intravenous zoledronic acid and oral alendronate in patients with a low trauma fracture: experience from an osteoporosis clinic  

191  JAK2 mutations in Asian patients with essential thrombocythaemia  
G-C. Wong, G. L. S. Kam and E. S. C. Koay

Brief Communications

197  Antitopoisomerase antibody positivity predates nailfold capillaroscopy abnormalities in scleroderma. Postulated classification of ‘prescleroderma’  
H. Englert, D. Champion, J. C. Wu, J. Giallussi, M. McGrath and N. Manolios

199  Atypical clinical presentations of the A3243G mutation, usually associated with MELAS  
S. Blum, T. Robertson, S. Klingberg, R. D. Henderson and P. McCombe
202 Rituximab-induced serum sickness in refractory immune thrombocytopenic purpura
G. Le Guenno, M. Ruivard, L. Charra and P. Philippe

Personal Viewpoint

206 Clinical effectiveness in everyday practice: improving outcomes for all patients through a national acute coronary syndrome data collaborative

Images in Medicine

210 Beware the glass-eyed patient with liver enlargement
A. Nini and M. Vardi

211 Left renal vein thrombosis causing left-sided varicocele
S. A. Pathiyaveetil and A. Mathew

Letters to the Editor

Clinical-scientific notes

212 Phaeochromocytoma, neurofibromatosis and gastrointestinal stromal tumour: just a random event?
S. K. Sandhu, P. McKenzie, B. Yu and E. Chua

213 Reversal of cardiomyopathy with ivabradine
B. Gray, P. Macdonald and D. Kuchar

General correspondence

215 Royal Australasian College of Physicians’ advanced training outside of Australia and New Zealand: trainees’ and supervisors’ perspectives
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Aromatase inhibitors: what is the true cost?

The major tenets of systemic anti-cancer therapy should be to improve either or both overall survival and quality of life with acceptable cost–benefit.

In this issue of the Journal, Vitry et al. discuss the rising costs associated with the use of aromatase inhibitors (AIs) in the treatment of breast cancer. As they point out, this class of drugs is now the preferred choice in Australia despite the lack of evidence of improvement in overall survival and the cost being six times that of the alternative drug, tamoxifen.

Tamoxifen, a selective oestrogen receptor modulator, has a proven survival benefit in the adjuvant setting, along with a well-understood side-effect profile that includes hot flushes (common) as well as deep vein thrombosis and uterine cancer at a combined rate of 0.2% per decade among women on treatment for 5 years. An overview of randomized trials of tamoxifen has shown an absolute improvement in survival of 9.2% at 15 years after diagnosis compared with no tamoxifen. For individual women the magnitude of benefit will vary with the risk of recurrence.

The AIs prevent the synthesis of oestrogen from adrenal produced androgen by blocking the aromatase enzyme. They are suitable only for postmenopausal women. Their side effects include hot flushes and arthralgia; the latter can affect 15–25% of women. AIs can cause a fall in bone mineral density (BMD) and a subsequent increased risk of fracture during treatment. This increased risk resolves after stopping treatment. Patients on an AI should have their BMD measured at baseline and every 2 years while on treatment. A fall in BMD or a low baseline can be treated with an oral or i.v. bisphosphonate, with their inherent toxicities and costs.

Adjuvant AI therapy has consistently been shown to be superior to tamoxifen in terms of disease-free survival (delaying recurrence) but has not been shown to improve overall survival. Ten-year survival data for 5 years of tamoxifen compared with 5 years of the AI anastrozole, the most mature AI trial to date, have recently been published. The absolute reduction in recurrence with anastrozole compared with tamoxifen was 4.3% at 10 years. There was no improvement in overall survival. The number of deaths after breast cancer recurrence in the anastrozole arm of the trial was reduced. However, the increase in the number of deaths from other cancers and other causes in those without breast cancer recurrence resulted in similar overall survival to tamoxifen.

Letrozole, another AI compared with tamoxifen in the adjuvant setting, now has 6-year data. An earlier interim analysis had shown an improvement in disease-free survival and subsequent unblinding allowed cross-over to the AI arm. Intention-to-treat analysis has not shown a significant improvement in survival. Subgroup analyses excluding patients who were allowed to cross-over are underpowered and post-hoc but do show a small advantage in this group. It may be that a true survival advantage exists but is likely now never to be proven. This will be an ongoing problem in oncology as primary outcomes other than overall survival are now frequent and these early results often prompt cross-over in trials.

Vitry et al. discuss the cost to the Pharmaceutical Benefits Scheme of the increase in prescribing of AIs. The true total cost of this treatment must include the cost of measuring, preventing and treating the effects on BMD, including the costs borne by patients of calcium and vitamin D supplementation and analgesia for arthralgia. This would seem likely to be more than the cost of managing the side effects of tamoxifen.

We know from the chemotherapy published work that breast cancer patients will accept side effects for even very small advantages in survival, but it is less clear whether they accept this for delayed recurrence alone. Certainly, the compliance with any adjuvant hormone therapy is known to be poor.

Aromatase inhibitors are not cheap. They offer a choice to women and their oncologists with regard to side-effect profile and have a role in delaying recurrence. They are just one example of new cancer treatments, often expensive, which provide improvements in disease-free survival in the adjuvant setting or progression-free survival in the metastatic setting but have no clear overall survival benefit. As a society, are we prepared to continue to bear the cost of these medications, or should we adopt a more hardline stance and only accept expensive new drugs if there is an improvement in quality of life and/or a clear and meaningful overall survival advantage?
Editorial

References

World Kidney Day 2011: protect your kidneys, save your heart

Introduction to World Kidney Day 2011

10 March 2011 will mark the celebration of the sixth World Kidney Day (WKD), an annual event jointly sponsored by the International Society of Nephrology and the International Federation of Kidney Foundations. Since its inception in 2006, WKD has grown dramatically to become the most widely celebrated event associated with kidney disease in the world and the most successful effort to raise awareness among both the general public and government health officials about the dangers of kidney disease, especially chronic kidney disease (CKD).

In 2011, WKD will call attention to the large, and often unappreciated, role played by kidney dysfunction in increasing premature cardiovascular disease (CVD), the most common cause of morbidity and mortality worldwide.1 Can a focus on early detection and prevention of kidney disease really improve long-term CV health? In this editorial, we hope to convey the message that increased attention to the kidneys can indeed improve long-term health outcomes by reducing both kidney and CV disease and should therefore be a central component of any global health strategy intended to reduce the enormous and growing burden of chronic noncommunicable diseases (NCD).

Cardiovascular disease and the kidney

Cardiovascular disease is the most common of the chronic NCD that influence global mortality. About 30% of all deaths worldwide and 10% of all healthy life lost to disease are accounted for by CVD alone.2 Although there has been some decline in mortality from CVD in developed countries, no such decline has been reported in developing countries, ethnic and socially disadvantaged minority populations or in people with accompanying CKD.2-3 The presence of CKD significantly increases the risk of a CV event in both diabetes and hypertension.4,5 However, less well appreciated is that CKD alone is a strong risk factor for CVD, independent of diabetes, hypertension or any other conventional CVD risk factor.6,7 This is especially true when an increase in proteinuria, a major target of any CKD screening programme, is present.6-10

The 20- to 30-fold increase in CVD in patients with end-stage renal disease (ESRD) has long been recognized, but the increased risk for CVD associated with lesser degrees of renal functional impairment was definitively demonstrated only in 2004. Go et al. reported an independent and graded association between glomerular filtration rate (GFR) and risk of death: CV events and hospitalizations were reported in a community-based study of over 1000 individuals.6 Is this dramatic increase in CVD risk associated with CKD really because of CKD or does it just reflect the coexistent diabetes or hypertension that is present in a majority of these patients? The independent effect of CKD alone has now been well documented in many studies.7 The risk of cardiac death is increased 46% in people with a GFR between 30 and 60 mL/min (Stage III CKD) independent of traditional CV risk factors, including diabetes and hypertension.10 The increased risk for CV events and mortality in people over 55 with CKD alone is equivalent, or even higher, to that seen in patients with diabetes or previous myocardial infarcts.11 Both general6,12 and high-risk populations13,14 show an increased risk of CVD with CKD. This increased risk for CVD is not confined to the elderly – in volunteers with an average age of 45, the risk for myocardial infarct, stroke and all cause mortality was doubled in those with CKD.14
Proteinuria and cardiovascular risk

In considering the value of recommending screening for CKD, along with conventional CVD risk factors in selected individuals, data showing that the risk of CVD is better correlated with proteinuria (albuminuria) than with the GFR alone is particularly relevant because proteinuria is virtually always a marker of kidney disease and is not a conventional CVD risk factor.21-23

With regard to proteinuria as a predictor of later CVD, the Prevention of Renal and Vascular Endstage Disease study showed a direct linear relationship between albuminuria and risk of CV death in the general population even at levels of albumin excretion generally considered within the ‘normal’ range (15–29 mg/day) and was increased more than sixfold when albumin excretion exceeded 300 mg/day.8

Recent data from the US national health and nutrition examination survey database as well as from Japan also document an independent effect of albuminuria on the risk of both CVD and all cause mortality at all levels of the GFR.15,16 In patients with congestive heart failure but without diabetes, hypertension or reduced GFR, increased urinary albumin predicts both CV and all cause mortality.17 Similar results are obtained studying patients with coronary disease or previous myocardial infarcts in whom proteinuria conferred a greater risk of mortality than reduced GFR, although both adversely impacted on the outcomes.18

Of interest, not only the likelihood but also the time to development of a CV event is accelerated significantly by the presence of proteinuria at all levels of the GFR.19 In non-diabetic subjects with normal serum creatinine levels undergoing percutaneous coronary interventions, about 78% have demonstrable CKD when screened more stringently for renal function (eGFR, urine protein).20 Not only is the presence of CKD a likely factor in accelerating development of coronary disease in these patients, but it has also been associated with an increase in other risks, including haemorrhagic complications, contrast nephropathy, re-stenosis and death.10 Thus, multiple studies now confirm that proteinuria is a graded risk factor for CVD independent of the GFR, hypertension and diabetes and that this risk extends down into ranges of albumin excretion generally considered ‘normal’.21,22 Moreover, this increased CV risk has been well demonstrated in several studies where only dipsticks were used to screen for increased protein excretion.6,18,21

Although there has been concern that CKD diagnosed by reduced GFR alone identifies predominately older adults at increased risk because of age alone,24 the connection between proteinuria as an independent risk factor for CV mortality has been confirmed by meta-analysis of 22 separate, general population, cohort studies and in both older (≥65) and younger people of several nationalities and racial groups.21

Can treatment of chronic kidney disease reduce cardiovascular disease?

Finally, and most importantly from a clinical perspective, there are provocative data to suggest that renal-targeted interventions designed to reduce proteinuria and slow progression of CKD can reduce CVD risk as well. Angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin receptor blocker (ARB) are of documented benefit in slowing progression of established diabetic and non-diabetic CKD.25-29 Of interest related to slowing progression, the incidence of CVD in CKD is significantly higher with more rapid loss of GFR independent of other risk factors, suggesting that interventions that slow progression may also reduce CVD.30 A 44% reduction in CV mortality over 4 years has been reported in patients screened from a general population with no risk factors except increased albumin in the urine and treated with renal-targeted ACEI therapy.30 This effect was seen primarily in people with albumin excretion rates of >50 mg/day in a pilot study, and the intervention was shown to be cost-effective in that population.11 CV endpoints were significantly reduced in direct proportion to the reduction of albuminuria with ACEI therapy, and albuminuria proved to be the only predictor of CV outcome.32 Other studies have also demonstrated that changes in proteinuria (in diabetics) better predict outcomes than changes in blood pressure (BP) achieved with ACEI therapy.13 The potential benefit of renal-targeted therapies has recently been highlighted by observations that higher doses of renin-angiotensin system (RAS) blockers than required for BP control alone can further reduce proteinuria independent of effects on BP or GFR, and that addition of salt restriction or diuretics, both very inexpensive interventions, can further enhance the proteinuria-reducing effect of RAS blockade.34,35 Data are not yet available to establish that screening for CKD and subsequent interventions will reduce CV mortality and be cost-effective in younger people (<55).36 However, it is now known that albuminuria is a better predictor of renal and CV events than blood pressure alone, that reducing proteinuria is more renal and cardio-protective than lowering blood pressure alone and that identification of CKD can improve CV outcomes.

Conclusion

As celebrations of the sixth WKD approach on 10 March 2011, it is worth noting that before the past decade, kidney disease was seen by most government and public
health authorities as largely confined to patients with ESRD, thankfully a rare condition because the enormous cost of renal replacement therapy disproportionately consumes scarce healthcare resources and is well beyond the means of countries inhabited by over 80% of the world’s population. Much has changed. We now appreciate that kidney disease is not rare—some 10% of the population has evidence of renal dysfunction. And we know these individuals are not of concern just because a few will progress to ESRD, but more because they carry a greatly enhanced risk of premature death from CVD, the single largest and most expensive healthcare threat we confront at a global level. Just as progress is being made in treating most of the traditional CV risk factors, CKD has emerged as yet another one that causes substantial vascular toxicity independently. Fortunately, there is good news as well. Biomarkers of CKD (proteinuria, eGFR) are easy and relatively inexpensive to detect, and one of these, proteinuria, emerges early in the evolution of generalized vascular disease. Thus, kidney-targeted detection and prevention programmes seem to offer a valuable opportunity to institute early preventive measures that go beyond traditional cardio-protective approaches. There is now compelling evidence that including selective screening for CKD in global health programmes designed primarily to reduce CVD will significantly improve the outcomes of not only renal disease, but especially the NCD like diabetes and CVD that dominate future healthcare strategies. Roadmaps for accomplishing this have already been presented for both developed and emerging countries. However, effective implementation of such strategies will only come when both the general public and the renal community work together to convince health authorities it is in the public interest to do this. It is our sincere hope that worldwide celebration of WKD 2011 will provide an opportunity to reinforce the message that kidney disease is indeed common, harmful and treatable and that protecting your kidneys is an important health strategy that may save your heart.

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For the joint International Society of Nephrology (WGC) and International Federation of Kidney Foundations (MCR) World Kidney Day 2011 Steering Committee* 

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References

Assessing individual clinical performance: a primer for physicians

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Key words
physician, performance, assessment, method.

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Abstract
The assessment of individual physician performance has attracted interest from several quarters, including statutory licensing agencies and credentialing bodies of healthcare institutions. Performance measures and assessment methods have been developed, although their validity, reliability and feasibility in regards to physician specialty practice are open to challenge. Despite this, professional colleges and societies will be increasingly obliged to ensure their members are demonstrating high-quality performance on the basis of assessment methods viewed as being transparent, impartial and reproducible. This article provides an overview of the current state of the art which hopefully will serve to inform future debate both within and outside professional circles.

Introduction
Clinical performance relates to what physicians actually do in everyday practice, with an emphasis on medical and technical expertise, while competence relates to what physicians are capable of doing in terms of knowledge, skills and attitudes.1 Assessment of competence at the completion of specialty training is reasonably well understood in terms of aims, scope and methods,2 and it can be assumed that consultant physicians recently conferred Fellowship have acquired an agreed set of competencies deemed necessary, by a professional society, for independent practice in the relevant discipline.

However, assessment of performance of individual physicians in practice is more concerned with measuring how they work and make judgements within complex and dynamic environments, apply knowledge, skills and attitudes to patient care independent of supervision, and acquire and apply new knowledge and skills throughout a long career. In this context, physicians can be ‘competent’, but not perform well. However, in reality, competence and performance are inter-related attributes in that poorly performing physicians may indeed be incompetent in some respects. In addition, methods of assessing competence and performance are likely to overlap in the move towards creating a seamless transition in assessment from training programmes to ongoing professional development and performance appraisal.

Why assess physician performance?
Performance assessment may have several purposes: identifying poorly or potentially poorly performing physicians; guiding professional development and helping all physicians to improve; and facilitating external validation for healthcare stakeholders.

There is evidence that performance of some physicians decays over time,1 and self-assessment is unreliable in the absence of more objective data from external sources.4 Without meaningful assessment, poor performance remains concealed and professional societies, medical boards, hospital credentialing bodies and other regulatory bodies are unable to identify, retrain and, if necessary, remove the very small minority whose performance has declined below an accepted standard. Professional self-regulation, if it is to remain free of external interference, requires transparent and credible performance assessment.

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Assessing of performance can also drive learning, professional development and performance enhancement of individual physicians. Assessment helps identify best clinical practices and evidence-practice gaps, knowledge of which can be shared more widely, as part of physician-led quality improvement programmes.

In various jurisdictions internationally, a focus on performance assessment is now emerging in concert with recertification or reviewal programmes (see Table 1). The drivers for recertification are multiple – economic, political, social and professional – and differ between countries. However, increasing awareness of clinician error and fallibility within care systems that are, at least partly, publicly funded has been a universal stimulus. Low participation rates in voluntary assessment and its failure to produce desired practice change have led to calls for more universal and effective review. It is probably no longer a matter of ‘if’ but ‘when’ mandatory recertification will be required for medical practice in developed countries.

**Challenges to performance assessment**

Depending on its purpose, assessment will be conducted from different perspectives and with different loci of control and intended outcomes. For example, assessment designed purely for professional development will be controlled by the individual, relatively inexpensive, and as valid and reliable as can be afforded. In contrast, assessment designed to protect patients will be controlled by external regulatory agencies, must have highest possible validity and reliability, and is likely to be resource intense. However, the common element in most assessment processes is review of practice conducted by professional peers.

A key challenge is determining the level at which performance is deemed to be acceptable. If maintaining a minimum standard of competence is the goal, then a minimum level of performance is all that is required. In contrast, if ongoing quality improvement is the goal, then the level of acceptable performance would periodically move upward to reflect overall improvement in performance over time.

But there are other challenges. First, studies of the long-term impact and effectiveness of continuous performance assessment of individual doctors are few. Observed changes in performance are small to moderate, and no study, as far as we are aware, has assessed impact on patient outcomes. Much of the literature focuses on assessment of competence of medical students and residents, rather than performance of specialty trainees and consultants. However, the Bundaberg and Garling reports would suggest that the absence of any formal performance monitoring of senior clinicians may engender poor practice. Second, the validity and reliability of many assessment methods of routine clinical performance await evaluation at a level sufficient to justify recommending their widespread use. For example, while some studies show quality of individual clinician care to be correlated with performance in generic tests of knowledge, diagnostic skills and clinical reasoning, critics argue that recertification processes should assess performance in actual practice by means of resource-intense testing that covers the highly individualized and specialized practice of most physicians.

No assessment method, by itself, is sufficiently robust psychometrically to make high-stakes, summative (i.e. pass-fail) assessment decisions relating to recertification. If recertification is the objective, a triangulation of information from multiple sources using different assessment methods applied by multiple peers will be required to produce reliable ratings of overall performance.

**What are the performance attributes that should be assessed?**

Performance attributes comprise a spectrum, from generic (i.e. all physicians should demonstrate them) to task-specific (i.e. specific to a specialized area of practice). Here the focus will be on generic attributes which are prerequisite for adequate performance and lie within the remit of colleges, such as the Royal Australasian College of Physicians (RACP), rather than task-specific competencies which are more the responsibility of specialty societies. With permission, we have adapted the framework of the Royal Australasian College of Surgeons and aligned it with the professional domains defined in the RACP Professional Qualities Curriculum in formulating eight generic competencies for physicians listed in Table 2.

This suggested framework does not necessarily constitute explicit standards of practice, is subject to further refinement, and the weightings given to individual competencies will vary according to the scope of practice of individual physicians and the settings in which they work.

**What tools exist for assessing physician performance and how good are they?**

Assessing the performance of practising consultants and trainees poses challenges at several levels. First, up until recently, no formal curriculum for physician trainees or Fellows existed which detailed the attributes of good performance. Second, much learning relies on passive
Recertification or revalidation initiatives in several countries7–15

<table>
<thead>
<tr>
<th>United States</th>
<th>United Kingdom</th>
<th>Canada</th>
<th>Australia</th>
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<tr>
<td>Recertification is voluntary but has been in operation for almost 20 years and most doctors, including specialists, choose to certify once they complete training through one of the American Board of Medical Specialty (ABMS) member boards. Since 1990, doctors who choose to certify after training must regularly recertify (every 5–10 years depending on the specialty) to retain board-certified status. Recertification: workplace-based process for specialists requiring demonstration of quality of practice using various forms of evidence: clinical audits, peer review, knowledge assessment, clinical outcomes data, multi-source feedback, directly observed procedural skills, and (for trainees) the mini-clinical evaluation exercise.</td>
<td>Revalidation: process for all doctors requiring participation in annual appraisals, peer and patient feedback, and continuing professional development (CPD); demonstration of no unresolved concerns about practice</td>
<td>No national recertification system currently exists. The Royal Australasian College of Surgeons has recently produced a list of desirable professional attributes for surgeons, linked with professional development resources and assessment methods. All surgeons are required to participate in a surgical audit each year and submit it for peer review.</td>
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For all specialties, the Maintenance of Certification process includes 4 elements: evidence of good professional standing (usually defined as an unrestricted licence to practise in a jurisdiction); participation in knowledge self-assessment; a pass–fail examination; and a practice audit and improvement exercise. In 2002, the ABMS required all 24 specialty boards to develop maintenance of certification programmes that would assess sets of competencies for practising physicians by 2010. The American Board of Internal Medicine also now requires self-evaluation of practice performance using its Practice Improvement Modules in order to maintain or renew certification. Quality assurance of the recertification process comprises psychometric validation of the pass–fail examination, with clinical reports being subject to audit.

Revalidation will be implemented in 2010 and will comprise the following mandatory processes:10

- Refocusing: process for all doctors requiring participation in annual appraisals, peer and patient feedback, and continuing professional development (CPD); demonstration of no unresolved concerns about practice.
- Recertification: workplace-based process for specialists requiring demonstration of quality of practice using various forms of evidence: clinical audits, peer review, knowledge assessment, clinical outcomes data, multi-source feedback, directly observed procedural skills, and (for trainees) the mini-clinical evaluation exercise.

Revalidation process will be regulated by the General Medical Council (GMC), with specialist standards and evidence for recertification set by the medical Royal Colleges. Evidence supporting revalidation will be discussed at annual appraisals and reviewed every 5 years by a locally based ‘responsible officer’ who will make recommendations to GMC about revalidation of individual physicians. The Royal Colleges and the GMC randomly audit documented evidence. No national recertification system currently exists although the issue is attracting debate. The Canadian Federation of Medical Regulatory Authorities, a national organization of the provincial regulators, recently issued a report supporting recertification that provided a set of guiding principles.11

The process for ensuring maintenance of clinical competence varies between the provinces and depends on the regulatory decisions of each provincial Royal College of Physicians and Surgeons (RCPs) that licenses physicians. The province of Alberta has mandated participation in the Physician Achievement Review as a requirement for continued licensure since 2001.12 In other provinces, physicians are required to participate in an educational programme, typically the RCPs’ Maintenance of Certification programme or the College of Family Physicians’ Maintenance of Proficiency programme to maintain licensure. These programmes require physicians to report, on an annual basis over a 5-year cycle, their participation in a variety of educational activities, with the colleges conducting random audits of the documentation. Several provinces also require a peer review process in which practice is assessed through office visits conducted by colleagues. The Royal Colleges randomly audit documented evidence.

Many of these initiatives have been informed by the Canadian Medical Education Directives for Specialists criteria14 and recently developed charters of professionalism.15 The Australian and New Zealand College of Anaesthetists has, of 2009, mandated its members to participate in a CPD programme that meets pre-defined learning objectives based on individual needs assessments, and which requires a minimum number of points in different categories of learning activities. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists requires mandatory participation in its CPD programme, incorporating a practice review and clinical risk management programme. The Royal Australian and New Zealand College of Psychiatrists requires mandatory participation in a CPD programme. The Royal Australasian College of Physicians has recently mandated participation in CPD programmes.

† Scott et al. 2011 The Authors Internal Medicine Journal © 2011 Royal Australasian College of Physicians

Table 1 Recertification or revalidation initiatives in several countries7–15
other healthcare professionals, and they interact with patients. All of these interactions ultimately determine health outcomes. How much should the performance of Microsystems and patients be assessed relative to the performance of the physician? Are systems and patients too often cited as an explanation (indeed justification) for suboptimal physician performance, requiring ‘adjustment’ in ‘no blame’ analyses, relieving physicians of at least some responsibility in care safer and of higher quality. Health advocacy: Responding to the health concerns of individual patients, families, carers and communities and demonstrating sensitivity to cultural, ethnic and spiritual needs. Collaboration and teamwork: Demonstrating skills in exchanging information, establishing shared understandings and playing an active role in clinical teams.

Performance assessment methods

Assessment methods can be categorized in several ways:

Implicit versus explicit measures

Implicit judgements rely on intuitive ratings or impressions while explicit measures are based on structured data to which explicit performance criteria or standards are applied. While some studies suggest an acceptable level of agreement between implicit and explicit assessments, other studies suggest that using structured assessment tools, checklists, and graded descriptors improves reliability of multiple peer review. Even if assessors are experienced clinicians, familiar with assessment processes, and undergo formal training, their ratings of peers tend to be inconsistent unless their reviews involve the use of structured assessment instruments. Consequently, explicit performance measures are generally preferred because of their reputedly greater objectivity and reliability.

Direct versus indirect assessment

Direct assessment involves evaluating practice or behaviour that has actually occurred, or is occurring, in real-world clinical practice. Some examples of direct observation methods include audit of medical notes, clinical registries or administrative datasets, standardized (incognito) patients, mini-clinical evaluation exercise (Mini-CEX) examinations, multi-source feedback, evidence-based practice logs or portfolios, sentinel (or significant) event analysis, direct observation of procedural skills in real-world settings, video-recordings of clinical interactions, and patient satisfaction interviews and surveys.

Indirect performance measures do not involve direct observation of practice and instead rely on assessment methods where a degree of arbitrariness or contrivance exists in the testing content. These include assessments using knowledge, skill and reasoning tests employing clinical vignettes (paper or computer based), objective structured clinical examinations, oral viva examinations (long and short cases), questionnaire surveys, high-fidelity simulation exercises, standardized patients (non-incognito) and some professional self-appraisal tools. Indirect measures may not accurately reflect what physicians actually do in daily clinical practice in contrast to the test setting and are not easily validated. However, some studies suggest that non-incognito standardized patients and clinical vignettes, when compared with direct measures such as chart review, show reasonably good correlation, and therefore constitute valid...
performance measures. Other indirect measures might include assessment of participation in professional development activities known to be effective in improving clinical performance, such as interactive, case-based, small group discussions with follow-up reinforcement.

An in-depth analysis of all available performance measures is beyond the scope of this article; the references already cited and several recent reviews provide more detail. In assessing performance, there is a growing preference for direct observation methods whose characteristics are summarized in Table 3. Table 4 provides examples of performance data that could potentially be obtained from clinical and/or administrative datasets.

Criteria for assessing utility of performance assessment methods

The usefulness of any assessment method will be a product of the following: acceptability, validity, reliability, educational impact and cost-effectiveness. Each of these attributes will be weighted differently according to the purpose of the assessment. For example, methods to detect poorly performing physicians must be highly sensitive and valid, while those aimed at improving or validating practice skills should show high validity, acceptability and educational impact. To be seen as credible, any measure should fulfil most, if not all, of the following criteria:

Agreed standards for satisfactory performance

The measure must have an established standard or threshold that delimits acceptable performance while minimizing the risk of misclassifying physicians as performing well or poorly. Reliability of assessment is directly related to the strength of the evidence base for the management of the clinical conditions being reviewed, and, in the absence of overwhelming expert consensus, declines when professional debate ensues over what constitutes appropriate practice. The paucity of widely accepted, evidence-based thresholds for minimal acceptable performance for many measures remains a major challenge to performance assessment. For some performance measures, an absolute threshold will exist such as 100% of all ideal candidates (i.e. no contra-indications) receiving aspirin after acute myocardial infarction (AMI). However, for most performance measures, an absolute threshold may not exist, or even if such a boundary does exist, it is likely to require further adjustment to account for other causes of less than perfect performance such as idiosyncratic patient reactions or patient choice. In such instances, some deviation from the 100% threshold must be accepted such as >80% but <100%. A more statistical approach is to define outliers as the bottom or top percentiles of a distribution, but draws criticism as being too arbitrary and unhelpful in situations in which performance across physicians is tightly clustered with only small differences between the bottom and top of the distribution.

Sound measurement properties

Validity and reliability of performance measures must be guaranteed according to:

Evidence-based and standardized specifications. Process-of-care measures will vary between medical specialties and need to be representative of the most commonly performed clinical activities of that specialty. Unfortunately, while some specialties, such as cardiology and endocrinology, have several evidence-based process measures, other specialties, such as palliative medicine and neurology, have comparatively few. The measure must also be capable of being collected in a reproducible fashion across multiple physicians and settings of care. Measures collected within, for example, high-quality clinical registries or structured electronic health records would easily meet this standard while data abstraction from paper-based records may not.

Adequate sampling. A sufficient number of different measures of performance must be used to ensure representative testing of an individual physician’s performance. The Joint Commission in the USA recommends at least 10 different measures per physician. For each chosen measure, the number of observations (or sample size) must be large enough to overcome the problem of random variation, especially in cases where assessment methods are not well standardized or reliable, that is, where the signal-to-noise ratio is low. In the case of disease-specific process-of-care measures (or indicators), individual physicians may have insufficient numbers of patients with particular conditions to enable accurate assessment. For example, at least 100 patients with diabetes per physician would be needed to achieve 80% reliability for most diabetes-related process-of-care measures. Achieving such numbers may be limited by patient exclusion criteria. For example, the proportion of patients with AMI considered ideal for reperfusion therapy ranges from 9% to 20%. Observations on patients of a single physician are also unlikely to be statistically independent due to patient clustering, which further inflates the sample size required to attain a satisfactory level of precision. Performance on a specific measure also appears to show little correlation with
Table 3 Qualities of different directly observed performance measurement instruments

<table>
<thead>
<tr>
<th>Measurement instrument</th>
<th>Advantages</th>
<th>Methodological aspects</th>
<th>Disadvantages</th>
<th>Overall utility</th>
<th>Performance attributes capable of being assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chart audits</td>
<td>Ready availability of charts; Combined with feedback can change clinical practice</td>
<td>Poor documentation may not accurately capture processes of care; Unable to assess quality of physician-patient interaction; Low reliability if based on implicit criteria; Resource intense; Resource intense; Needs to update audit indicators according to newly released guidelines</td>
<td>++</td>
<td>++</td>
<td>Clinical expertise (technical expertise); clinical decision-making</td>
</tr>
<tr>
<td>Direct observation of practice (practice visits)</td>
<td>High face validity; Can encompass assessment of different aspects of practice in one visit</td>
<td>Paucity of evidence about validity and reliability of observers if not appropriately trained; Resource intense</td>
<td>++</td>
<td>All</td>
<td>Clinical expertise (technical expertise); communication; professionalism</td>
</tr>
<tr>
<td>Standardized patients</td>
<td>High level of reliability due to case standardization; Perceived as real patients if randomly presented to physicians unannounced; Able to assess different professional attributes within one encounter</td>
<td>May need several types of cases with varying levels of complexity to adequately assess performance; Less efficient in assessing clinical reasoning if post-encounter questions about diagnosis and management are not included; Resource intense due to training requirements</td>
<td>+++</td>
<td>++</td>
<td>Clinical expertise; clinical decision-making; communication; professionalism</td>
</tr>
<tr>
<td>Video observation of practice</td>
<td>High face validity; Allows repeated playback and analysis of specific clinical interactions; Can be archived for future review if necessary; Provides educational feedback and is useful for teaching; May have particular application to assessing procedural skills</td>
<td>Potential Hawthorne effects unless video recorder is concealed and recording occurs at random; Ethical concerns around patient privacy; Acceptability to physicians may vary</td>
<td>++</td>
<td>Clinical expertise (technical expertise); communication; professionalism</td>
<td></td>
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<tr>
<td>Mini-clinical evaluation exercise</td>
<td>Standardized scoring template which takes 30 min to complete</td>
<td>May be confounded by Hawthorne effects and observer bias; Needs 6–10 exercises per physician to generate consistent ratings of performance due to inter-rater variability; Limited content specificity; Takes time</td>
<td>+++</td>
<td>+++</td>
<td>Clinical expertise; clinical decision-making; communication; professionalism</td>
</tr>
<tr>
<td>Multi-source feedback (360° interviews with colleagues, patients)</td>
<td>Ability to assess different professional attributes using several colleagues from different disciplines; Based on collective observations over an extended period of time; Ease and rapidity of use of feedback questionnaire; Does not require large numbers of surveys</td>
<td>May be confounded by recall and observer bias; Reasonably resource intense as it ideally requires more than 10 observers per physician; High levels of inter-rater variability may be seen for specific performance attributes; Needs to be based on high levels of personal and organizational trust</td>
<td>++</td>
<td>All</td>
<td>Clinical expertise; clinical decision-making; communication; professionalism</td>
</tr>
<tr>
<td>Significant incident analysis</td>
<td>Usually well documented and relate to clinically important events; High impact factor on physicians with potential for practice change; Time to assess thoroughly</td>
<td>Infrequent occurrences; May result from factors outside control of individual physicians; May have medico-legal ramifications which inhibit tacit and open discussion; Requires robust and consistent approach in order to be meaningful</td>
<td>+</td>
<td>Clinical expertise; clinical decision-making; professionalism; learning and teaching</td>
<td></td>
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<tr>
<td>Evidence-based practice logs or portfolios</td>
<td>Ability to assess the use of clinical question formulation, literature searches, critical appraisal, and application of research evidence in routine clinical practice; Ease and rapidity of use</td>
<td>Assessment methods have focused on medical students and residents – applicability to consultants unclear; Relies on self-report, which may be subject to bias</td>
<td>++</td>
<td>Clinical expertise; clinical decision-making; teaching and learning</td>
<td></td>
</tr>
<tr>
<td>High-fidelity procedural simulations</td>
<td>Ability to assess procedural skills with high accuracy and no risk of patient harm; Early identification of deficiencies in psychomotor and manual dexterity skills</td>
<td>Highly resource intense (mannequins, procedural simulators, virtual reality simulators); Restricted access to simulation laboratories; High level of expertise required of assessors</td>
<td>++</td>
<td>Technical expertise</td>
<td></td>
</tr>
<tr>
<td>Patient satisfaction survey</td>
<td>Ability to assess communication and professional skills; Relates directly to enduser of healthcare</td>
<td>Potential for self-referential bias whereby patient’s frustration with illness or impairment may colour attitudes towards health professionals; alternatively halo effect and/or reluctance to be seen as criticizing person providing care which might provoke withdrawal of care; Multiple potential drivers of patient satisfaction which vary beyond the control of individual physicians</td>
<td>+</td>
<td>Communication; health advocacy; professionalism</td>
<td></td>
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†Psychometric soundness rated as +++ if multiple studies in different populations and settings show consistently valid and reliable results; ++ if 2 or 3 studies in at least two independent samples, which provide estimates of validity and reliability; + if single or no studies have been performed. Overall utility is rated +++ if all three criteria of validity, reliability and feasibility apply; ++ if valid and reliable, but not reliable; + if reliable and feasible but not validated.
performance on other measures for different clinical conditions.\textsuperscript{70,71} Composite measures (a combination of several individual measures) may allow more physicians to be evaluated reliably for a given patient sample, but are less interpretable and actionable as they conflate what may be quite different performance measures.\textsuperscript{27} One potential solution to problems of small samples is the use of statistical process control (SPC) methods which confer high sensitivity in detecting unfavourable trends concerning uncommon adverse outcomes.\textsuperscript{72}

Adjustment for confounding patient factors. Comparisons with benchmarks or other physicians may be confounded by differences between patient populations of different physicians or with the population from which the benchmark was derived. Such differences relate to variations in illness severity, comorbidity, or access to care services. In general, potential confounding bias may be minimized by risk adjustment or restriction. However, both strategies are imperfect, often requiring detailed clinical information specific for a particular clinical condition.\textsuperscript{73} Such data collection on a large scale is costly and difficult to validate. Risk adjustment methods that rely on routinely collected administrative data, while perhaps reasonable for research purposes and quality improvement, may not be precise enough to evaluate accurately individual performance. Restricting analyses to ‘ideal’ patients (strong indication for an intervention with no contraindications) reduces patient heterogeneity, but requires consensus around eligibility criteria for the care in question, and resource-intense chart review in determining patient eligibility.\textsuperscript{63}

**Psychometric properties.** Validity is the extent to which the instrument measures what it purports to measure. Reliability refers to the instrument’s inherent measurement error (or signal to noise ratio) and includes internal consistency, test–retest reliability (or reproducibility), and intra-rater and inter-rater reliability in the case of single or multiple assessors of performance respectively. Discrimination describes the ability of the instrument to distinguish between physicians with different levels of performance. Response process refers to evidence of raters having been properly trained, although randomized trials indicate that, beyond a minimum amount of instruction, additional training achieves little further improvement in accuracy or reliability of scores.\textsuperscript{74,75} Ideally, there should be evaluative evidence for each of

<table>
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<tr>
<th>Table 4 Performance measures obtained from clinical or administrative datasets</th>
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<tbody>
<tr>
<td><strong>Process measures</strong></td>
</tr>
<tr>
<td>Compliance with care guidelines and protocols</td>
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<tr>
<td>Patterns of test, drug or procedure utilization</td>
</tr>
<tr>
<td><strong>Outcome measures</strong></td>
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<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Readmissions</td>
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<tr>
<td>Length of stay; physician-attributable avoidable patient days</td>
</tr>
<tr>
<td>Complications</td>
</tr>
<tr>
<td>Adverse/sentinel events</td>
</tr>
<tr>
<td>Medication prescribing errors</td>
</tr>
<tr>
<td><strong>Quantity of clinical audits or case reviews undertaken</strong></td>
</tr>
<tr>
<td><strong>Quantity of clinical audits or case reviews showing inappropriate care</strong></td>
</tr>
<tr>
<td><strong>Quantity of clinical guidelines, care protocols, decision rules and other forms of decision support created or accessed</strong></td>
</tr>
<tr>
<td><strong>Quantity of use of evidence sources in answering clinical questions</strong></td>
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<tr>
<td><strong>Level of participation in CPD programmes</strong></td>
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<td><strong>Quantity of patient/family complaints</strong></td>
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<td><strong>Quantity of patient/family compliments</strong></td>
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<tr>
<td><strong>Patient satisfaction survey performance</strong></td>
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<tr>
<td><strong>Quantity of peer complaints</strong></td>
</tr>
<tr>
<td><strong>Quantity of peer compliments</strong></td>
</tr>
<tr>
<td><strong>Quantity of discharge summaries and reply letters to referring doctors</strong></td>
</tr>
<tr>
<td><strong>Appropriate referrals to other consultants</strong></td>
</tr>
<tr>
<td><strong>Level of involvement in professional activities (apart from day to day clinical care)</strong></td>
</tr>
<tr>
<td>such as committees, trainee education, etc</td>
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</table>

CPD, continuing professional development.
the properties listed above for any chosen assessment method. However, a recent review concluded that only 10 of 55 assessment methods were associated with such evidence.58

**Attribution accuracy and controllability**

Results of any performance measure pertaining to an individual physician must be fully or predominantly attributable to the actions of that individual. In cases where individual attribution is disputed, then performance data should be amenable to ‘benefit of the doubt’ analyses in which disputed cases have been removed. Performance measures that relate to processes of care should focus on those processes that are, at least partly, under control of the physician.29 In addition, any thresholds or performance targets should be achievable given the logistical resources available to that physician.

**Timeliness**

Performance measures must be capable of providing real-time analyses of contemporary datasets, that is, preferably no more than 6–12 months old. Applying SPC methods to datasets may serve to stress unfavourable trends in individual physician practice earlier than would be the case using conventional statistical methods.72

**Metric balance**

There should be a reasonably equitable distribution of the measures across each of the eight performance attributes, with clinical expertise and decision-making receiving higher weightings. However, not all measures will have equal validity; chart audits are resource-intensive, but provide valid information whereas patient satisfaction tools are cheap, but have questionable validity in assessing quality of technical care, although perhaps more reliable in assessing communication skills and attributes of ‘patient-centredness’ and ‘timeliness’.77,78 Assessing how well physicians collaborate with others in achieving desired outcomes (teamwork), improve patients’ knowledge and understanding of their health (patient empowerment), keep up to date with new developments (currency of practice), and appreciate their strengths and weaknesses (insight) is currently underdeveloped and in need of agreed definitions and clear assessment methods.21

**Feasibility, ease of use and sustainability**

Performance measures must be feasible to collect in an efficient and reliable manner over the long term. Large-scale clinical registries or hospital-level quality initiatives that include clinical data may be reasonably affordable, particularly if physicians practise wholly or predominantly in one site. However, for private physicians who visit multiple clinics or small facilities, such data collection will be substantially more expensive and the cost borne personally. Increasing availability of electronic medical records and automated laboratory data may mitigate some of these expenses in the future. While discrete outcomes and some processes of care are readily measurable, functional status, which may be more relevant to some specialties such as rheumatology or neurology, is more problematic, especially over long periods of follow up.

Performance data need to be fed back in a timely fashion, using visual formats for more intuitive comprehension, and rendered accessible to individual physicians. Data should also be customisable according to specialty, selected time periods and patient sub-groups, and able to be viewed in aggregate or drill-down formats in providing more detail of underlying trends, adjusting data for various factors if possible, and presenting comparative performance against agreed benchmarks.

**Monitoring for unintended adverse consequences**

Performance measurement may, in a few individuals, evoke refusal to provide data, gaming of the data, or even outright fraud. Rules around mandatory participation and careful auditing of data have to be part of any measurement and reporting system. Another concern is that physicians may start to focus their efforts on areas being directly measured to the detriment of other aspects of care not being monitored. Authorities have recommended including measures that assess a wide spectrum of care, which, to be sustainable, may require rotating through a set of measures over a cycle of assessment.79

**Where to from here?**

The above discussion indicates a current dearth of robust, fit for purpose tools for assessing physician performance in routine clinical practice. However, it is unlikely, given the worldwide momentum behind recertification, that the RACP will have time (let alone the resources) to research and validate assessment tools that cover the varied contexts of physician practice.

Perhaps, in the first instance, it is important that the curriculum for physician training sets explicit standards of competency and uses evaluative methods, such as those mentioned, that more faithfully, if not perfectly, assess such standards. At the present time, in regards to the physician training programme – Preparing for Professional Practice – the RACP Education Deanery has
Table 5 Direct observation methods for assessing physician performance adopted in the Royal Australasian College of Physicians – Preparing for Professional Practice training programme

<table>
<thead>
<tr>
<th>Methods</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Significant event analysis</td>
<td>This exercise requires the physician to examine a significant incident that has occurred in practice and has impacted on the quality of care provided. The physician, using a structured analysis sheet, has to reflect on what happened and why, the learnings from the incident and how future care might be improved, and what actions must now occur to improve quality. The completed analysis sheet is then reviewed by a senior colleague who then meets the physician for a debriefing session and affirmation of the intended improvement plan.</td>
</tr>
<tr>
<td>Mini-clinical evaluation exercise</td>
<td>The mini-clinical evaluation exercise involves direct observation of 15- to 20-min interviews and examinations as undertaken by physicians in real-world clinical settings. Professional performance relating to history taking, examination skill, attitudes to patients, communication skills and clinical reasoning is scored on a standardized form and then totalled. The instrument has been well studied and demonstrates high levels of internal consistency and construct validity in undergraduate and vocational training settings.</td>
</tr>
<tr>
<td>Multi-source feedback</td>
<td>Multi-source feedback (sometimes termed 360° evaluation if it includes non-physicians, rate using Likert scales) an individual’s performance in terms of leadership style, ability to lead and work in teams, communication skills, clinical judgement, and professionalism. The results of this structured assessment are then fed back anonymously to the individual. The validity of the observations rests on impartial comments based on observing everyday behaviour over an extended period of time.</td>
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The RACP and specialty societies will need to ensure that ongoing professional development and performance assessment for practising consultants place more emphasis on quality and safety dimensions of care, and self-improvement processes within individualized practice contexts that feature considerable experiential learning. Assessment methods are needed, which, while inadequate as summative assessments for individuals, encourage physicians to be more aware of, and responsive to, potentially remediable deficiencies in clinical performance. Guidelines exist which enunciate the steps that professional societies should follow in developing and implementing performance assessment programmes, which are seen to be fair, robust and defensible.

Table 6 Factors critical for success in performance assessment programmes

<table>
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<tr>
<th>Factors</th>
<th>Description</th>
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<tbody>
<tr>
<td>Performance assessment needs to be viewed as a means for assessing and potentially improving patient care across the board, not as a potentially punitive exercise aimed solely at a very small minority of poorly performing individuals. Physicians need to be actively involved in choosing assessment methods and specifying performance benchmarks, be adequately trained in the use of assessment methods, and be fully aware of their limitations. The professional attributes regarded as important by the Fellowship must be the targets for assessment, even though this may pose methodological challenges for many assessment instruments. Sufficient resources and physician time must be made available to allow adequate collection and analysis of data, feedback and debriefing involving those being assessed, and input of assessment results into ongoing individual learning portfolios and professional development plans. As much as possible, assessment methods must not be unduly burdensome and use information and data that physicians already collect, or can collect in the future with a minimum of effort and expense. Currently available assessment methods should be used for formative purposes (professional development and improvement) rather than summative purposes (recertification) until they attract more robust evidence of validity and reliability. Multiple assessment methods involving multiple reviewers and a variety of data sources are preferred to single or a small number of methods and/or data sources in order to overcome the respective problems of content (or skill) specificity and bias or inaccuracy involving data sources. Achieving high sampling rates for several different assessment methods, even if they are not highly standardized, probably gives a more accurate picture of overall performance than relying on a small number of methods which, while highly standardized and reliable, are associated with lower rates of sampling. Methods for assessing performance applied to both trainees and consultants should be similar in format, coverage of behaviours and means of application in order to create a seamless, continuous line of assessment throughout professional life. The proactive identification of the relatively few cases of behaviours which are clearly unprofessional or suggest grossly impaired performance should continue in parallel with the evolving implementation of more refined methods of performance assessment.</td>
<td></td>
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</tbody>
</table>
Conclusion

If performance assessment is to be acceptable and of value to physicians, our review of available evidence, coupled with advice from educational experts, would suggest the factors listed in Table 6 to be critical to success.

Acknowledgement

The authors thank Karen Steadman from the RACP Quality Expert Advisory Group for assistance in providing data on current revalidation programmes of Australian specialty colleges.

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Assessing clinical performance

65 The Joint Commission. Proposed Revisions to the Medical Staff Credentialing and Privileging Standards, November 2005.
Dopamine agonists in the treatment of prolactinoma: are they still first choice?

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Reproductive Endocrine Group at Fertility Associates, Auckland, New Zealand

Abstract

Dopamine agonist therapy has been the cornerstone treatment for prolactinoma since the 1970s, replacing surgery in the primary management of this condition. These agents are effective in the management of prolactin excess, have a low side-effect profile, and in some cases may even be curative. However, recent studies of high dose dopamine agonists used in Parkinson’s disease have raised the possibility that these drugs may be associated with cardiac valvulopathy. This paper discusses the modern use of dopamine agonists in a patient with prolactinoma.

Introduction

Pituitary adenomas occur in up to 10% of the population, albeit often undiagnosed in life, and 70% secrete prolactin. Symptoms of a prolactinoma depend on size and level of hormone secretion. Large tumours may present with mass effects, such as headache, visual field involvement and ophthalmoplegia. More commonly, a patient with prolactinoma presents with galactorrhoea or symptoms of hypogonadism. The treatment of choice is judicious use of a dopamine agonist with or without replacement gonadal steroids, usually for some years of follow up, although a minority of tumours may resolve in time. While long-term safety and efficacy of these agents have been widely accepted, recent data linking dopamine agonist treatment with cardiac valve abnormalities has caused concern amongst endocrinologists. While most data relating to cardiac valve abnormalities is from studies of patients with Parkinson’s disease who receive high cumulative doses of a dopamine agonist, more recent publications have examined the risk of valvulopathy in prolactinoma patients. It is timely to review the pros and cons of dopamine agonist treatment in prolactinoma with this new information.

Prolactinoma

Micro (<10 mm) and macroprolactinomas (>10 mm) are the most common cause of primary hyperprolactinaemia. The diagnosis is confirmed by gadolinium-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) with contrast if MRI is unavailable or contraindicated. CT is less sensitive than MRI for diagnosing smaller adenomas and in defining the extent of larger tumours. Ten to twenty per cent of normal populations have non-functioning pituitary microadenomas (incidentalomas) and scan findings should be interpreted in association with the biochemistry and symptoms to avoid over diagnosis. Macroprolactinomas are generally associated with prolactin levels of at least 4000 mIU/L (200 μg/L). A large tumour with only a minimally raised prolactin level should always raise the possibility of stalk compression from a non-functioning tumour.

Treatment of prolactinoma

Principles

Dopamine agonist therapy is the cornerstone management of a prolactinoma and should be regarded as potentially curative therapy. With the advent of dopamine agonists, pituitary surgery has become uncommon except in the setting of apoplexy and impending loss of vision, non-compliance, intolerable side-effects from
medication, resistance to medical therapy or doubt as to diagnosis. In premenopausal women, dopamine agonist therapy is titrated until symptoms resolve, prolactin levels normalize, tumour shrinkage is demonstrated and menses or pregnancy occurs. Formal visual field assessment at baseline and during treatment is mandatory in the presence of a macroprolactinoma involving or adjacent to the optic chiasm.

Men with hyperprolactinaemia present with low libido, erectile dysfunction, poor sperm count and/or mass symptoms. Treatment principles are similar to women. In addition to the expected reduction in tumour size and mass symptoms, improvement in erectile function, semen quality and testosterone levels have been documented as late benefits of dopamine agonist treatment once prolactin levels are corrected.3

Dopamine agonists

Dopamine agonists used in the management of hyperprolactinaemia include bromocriptine, cabergoline, quinagolide, lisuride and pergolide. These medications are summarized in Table 1. Bromocriptine and cabergoline are the two ergot-derived dopamine agonists most commonly used in the management of hyperprolactinaemia. Bromocriptine is an ergot alkaloid with agonist action on the D2 receptor and was the first dopamine agonist to be utilized for the treatment of prolactinoma, having been in clinical use since 1973. Most prolactinomas will respond to low dose bromocriptine treatment (e.g. 2.5–5 mg daily) but the dose can be increased up to 30 mg daily if required. The dosage of bromocriptine is titrated to achieve optimal levels of prolactin while minimizing side-effects.

Cabergoline is a long acting dopamine receptor agonist with high affinity to the D2 receptor, and hence the dosage is less than bromocriptine (generally 0.5–4 mg taken once or twice weekly in divided doses). Cabergoline is also used for treatment of Parkinson’s disease but in much higher dosage (up to 25 mg/week).

Quinagolide is a non-ergot, well-tolerated D2 receptor agonist available in Australia but not in New Zealand. Quinagolide is given once daily, utilizing a starter pack to gradually increase the dose to maintenance dose of 75 µg daily. If necessary, the dose can be increased up to 300 µg daily to normalize prolactin levels.

Lisuride is an ergot derivative with agonist action at the D2 receptor, administered three times a day, up to 2 mg daily, and occasionally in higher dose. Side-effects, particularly nausea may limit compliance. It is not available in Australia but used in the UK and some parts of Europe. Pergolide was the first dopamine agonist to be associated with valvulopathy and has now been withdrawn from use in the USA and is not available in Australia. It is still funded for use in New Zealand.

Cabergoline and quinagolide have fewer side-effects than other dopamine agonists, and cabergoline has shown greater efficacy in suppression of prolactin and reduction of tumour size than bromocriptine.4 Cabergoline and quinagolide are more expensive than bromocriptine, and their availability is limited in some countries. If a pregnancy is being considered, we use bromocriptine as the dopamine agonist of choice as there is significantly more documentation of the safety of bromocriptine with regard to the fetus than with other dopamine agonists. The literature has reported on over 6000 children conceived on bromocriptine.5 If a patient is intolerant of or resistant to bromocriptine, cabergoline is a reasonable second choice.

Cabergoline in conventional doses (0.25–4 mg/week) achieves normalization of prolactin levels in approximately 75–80% of prolactinomas; bromocriptine is

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dopamine receptor sensitivity</th>
<th>Typical prolactinoma dose</th>
<th>Side-effects</th>
<th>Risk of valvulopathy for doses described</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>D1 antagonist, D2 agonist</td>
<td>2.5–7.5 mg/day</td>
<td>Nausea, nasal stuffiness, dizziness, headache, drowsiness common for all. Less common – digital vasospasm, insomnia, mood change</td>
<td>Low</td>
<td>First-line treatment especially if wanting pregnancy</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>D2 selective agonist</td>
<td>0.25–4 mg/week</td>
<td>Possible, more evidence required</td>
<td>Low</td>
<td>First-line treatment option Available in Australia but not in NZ</td>
</tr>
<tr>
<td>Quinagolide</td>
<td>D2 selective agonist</td>
<td>75–300 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisuride</td>
<td>D2 selective agonist</td>
<td>Up to 2 mg/day</td>
<td>Low – no 5HT(2B) agonist activity but few studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pergolide</td>
<td>D1 and D2 agonist</td>
<td>Not clinically used for prolactinoma treatment in USA/Australia/NZ</td>
<td>Withdrawn from USA due to this complication</td>
<td></td>
<td></td>
</tr>
</tbody>
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157
slightly less effective, achieving normal prolactin levels in approximately 60% of women,\(^4\) dependent on tumour size and pretreatment with other agents. The majority of prolactinomas respond quickly to dopamine agonists with obvious change in tumour size on MRI scanning after 2–3 months of treatment (Fig. 1). Timing of a repeat scan is dependent on initial tumour size, complicating mass symptoms and desire for fertility. Approximately 10% of cabergoline treated patients and 20% of bromocriptine treated patients may demonstrate partial or complete resistance to medical therapy,\(^6\) although recent studies have suggested that in some patients, this may reflect insufficient dose of dopamine agonist.\(^7\)

In the longer term, dopamine agonist therapy is associated with complete regression of both micro and macroadenomas in around 20% of men and women.\(^8\) In a meta-analysis of 19 studies, persisting normoprolactinaemia is more likely if patients have been treated for idiopathic hyperprolactinaemia, if treatment duration is of more than 2 years, or if cabergoline has been used.\(^8\) Withdrawal of dopamine agonist therapy is reasonable once 2–4 years of treatment have been completed if prolactin levels have normalized on low dose treatment and there is minimal radiological evidence of tumour on MRI scanning. Monitoring of prolactin levels should continue for 2–3 years post withdrawal of dopamine agonist.\(^6\) If therapy needs to be reinstituted, further attempts at withdrawing medication can be made in another 2 years if prolactin levels have been well suppressed after the second trial of dopamine agonist treatment.

**Side-effects**

Dopamine agonist therapy is associated with immediate side-effects of nasal stuffiness, postural hypotension and nausea in about 10% of patients on bromocriptine and in 1–5% of cabergoline treated patients.\(^9\) Symptoms usually settle with time, gradual upward adjustment of dose and

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**Figure 1** Pituitary magnetic resonance imaging demonstrating (a) coronal and (b) sagittal view of 14-mm prolactinoma at time of diagnosis. (c) Coronal and (d) sagittal view demonstrate complete resolution of the prolactinoma after 12 months of cabergoline therapy.
medication administration at night and with food. In addition, during postmarketing surveillance, cases of aggression and psychotic disorder have been reported in patients taking cabergoline and caution is advised in patients with a significant history of psychosis or mood disorder.10

A new concern is that dopamine agonists, particularly cabergoline, may increase the risk of heart valve abnormalities.11 Certainly, there is biological plausibility in this theory as cabergoline and pergolide in particular stimulate the cardiac valve 5HT2B receptor implicated in dexfenfluramine-related valve fibrosis.12 Bromocriptine and quinagolide have weaker affinity for this receptor and are thought to be less likely to cause valve fibrosis.

Over the past decade, there were occasional case reports of valvulopathy in the setting of cabergoline or pergolide when used in high dose for the treatment of Parkinson’s disease, and in 2007, two major studies were published supporting an increased risk of valvulopathy in this clinical setting.13,15 In a cross-sectional study of 155 Italian patients with Parkinson’s disease, clinically important regurgitation was found in 23.4% of pergolide-treated patients, 28.6% of cabergoline-treated patients, 0% of patients treated with other dopamine agonists and in 5.6% of controls. A dose–response was also found, as patients who had received the highest cumulative dose of cabergoline or pergolide were more likely to have significant valvular regurgitation (grade 3 or 4).13 The cumulative total dose of cabergoline used in Parkinson’s disease ranged from 2500–6700 mg compared with 200–500 mg to treat patients with prolactinoma. A second nested case–control study of Parkinson’s patients was published in the same year, comprising data from a UK general practice database, and determined an increased rate of cardiac valve regurgitation with pergolide (incidence-rate ratio 7.1) and cabergoline (incidence-rate ratio 4.9) but not with other dopamine agonists.12 The adjusted incidence-rate ratios were particularly concerning for doses of more than 3 mg per day of cabergoline or pergolide as well as dose duration longer than 6 months (i.e. total cumulative dose >540 mg). Two further Japanese studies confirmed the association of the cumulative dose of cabergoline and risk of significant valve regurgitation in patients with Parkinson’s disease.14,15 Pergolide was withdrawn from the USA market that year as a consequence of these reports.

Could the risk of valvulopathy extend to the lower doses of cabergoline used to treat hyperprolactinaemia?

A recent meta-analysis of nine observational studies comprising 639 prolactinoma patients treated with cabergoline provides the most comprehensive review of the literature thus far.16 This meta-analysis of dopamine agonists and their effect on cardiac valve function is in fact largely reassuring. The nine studies vary in size, choice of controls, grading of echo findings, and number and blinding of the echocardiographers who assessed cardiac echo results. One relatively small Italian study of 50 patients treated with cabergoline showed an increased prevalence of asymptomatic tricuspid regurgitation (54% in prolactinoma patients compared with 0% in staff controls and 18% in untreated prolactinoma patients) but possible confounders included more hypertension in the study group (a known risk for cardiac valvulopathy) and an uncertain number of echocardiographers reporting the cardiac echo findings.15 In this study, the cumulative dose of cabergoline was 414 ± 390 mg (mean ± SD) in patients treated for 16–260 months (median 74 months). In the remaining eight studies comprising 589 cabergoline-treated prolactinoma patients, there was no association between cabergoline therapy and significant valvulopathy.16 Randomized data from larger trials are required to prove or completely disprove an association between the usual doses of dopamine agonists used in the management of hyperprolactinaemia and valvulopathy.

What is the best advice to current or potential patients on dopamine agonists?

Whilst the data discussed for hyperprolactinaemic patients is largely reassuring, it seems prudent to inform patients of the small possible risk of valvular lesions, perform a cardiovascular examination prior to starting therapy and monitor clinically or by serial (1–2 yearly) echocardiography (if available), especially in patients who require higher dose and/or long-term therapy with dopamine agonists. Regular consideration should be given to a trial of therapy withdrawal and keeping dopamine agonist dosage to a minimum. Bromocriptine or quinagolide can be discussed as alternatives to cabergoline, depending on patient preference, availability, side-effects and/or desire for pregnancy.

There have been rare reports of pulmonary and retroperitoneal fibrosis secondary to bromocriptine and cabergoline,18 so regular clinical review of patients, continued assessment of the need for treatment and optimizing dose remain important.

Alternative treatments to dopamine agonists

The oral contraceptive pill (OCP) is an alternative to dopamine agonist therapy in premenopausal women with a microprolactinoma, providing contraception and potential protection from oestrogen deficiency symptoms.
and bone loss. While there are theoretical concerns that oestrogen may stimulate further growth of lactotrope adenomas, in practice, data that the OCP causes an increase in prolactinoma size is less than convincing. However, if a dopamine agonist is not utilized, prolactin levels should be closely monitored as a guide to potential tumour growth and patients rescanned 12 months after withdrawal of therapy or if prolactin levels rise significantly.

Trans-sphenoidal surgery and radiotherapy are reserved for cases that demonstrate pharmacological intolerance, non-compliance or resistance (defined as a failure to normalize prolactin levels and/or a failure to decrease prolactinoma size by 50%). Surgery can induce long-term normoprolactinaemia in 85% of microprolactinomas resistant to dopamine agonist therapy but remission in macroprolactinomas is less common and is dependent on initial prolactin levels and the invasiveness of the prolactinoma.

**Ovulation induction**

Hyperprolactinaemia is an eminently treatable cause of delay in fertility and should not be overlooked. Dopamine agonist therapy is first line for hyperprolactinaemic women desirous of pregnancy, and is very effective for ovulation induction. Ovulation returns on average about 6 weeks after normalization of prolactin. A minority of women (10%) require additional clomiphene citrate or gonadotropin therapy to induce ovulation successfully.

**Prolactinomas in pregnancy**

Prolactin levels rise in normal pregnancy, and larger untreated tumours are at risk of expansion because of oestrogen stimulation. Bromocriptine is the dopamine agonist of choice in women desirous of pregnancy and is very effective for ovulation induction. Ovulation returns on average about 6 weeks after normalization of prolactin. A minority of women (10%) require additional clomiphene citrate or gonadotropin therapy to induce ovulation successfully.

Menopause

There are limited retrospective data to provide advice on the management of women with either micro or macroprolactinoma after menopause. In clinical practice, most endocrinologists would withdraw dopamine agonist therapy in a postmenopausal woman, but monitor prolactin levels annually, unless there is significant tumour bulk remaining on imaging where a decision may be made to continue with therapy.

**Lactotrope hyperplasia**

Some women have no documented secondary cause for hyperprolactinaemia and are assumed to have hyperprolactinaemia secondary to a very small microprolactinoma or lactotrope hyperplasia. They are managed as if they have a microprolactinoma.

**Conclusion**

Over the past decade, the development of effective and well-tolerated dopamine agonists has allowed...
endocrinologists to manage the majority of prolactinoma patients without surgery. In addition, a significant proportion of patients with lactotrophe hyperplasia or adenoma can expect complete resolution of their pituitary tumour. Recently there has been some concern that these effective endocrine agents could cause cardiac valvulopathy, based primarily on observational data from patients with Parkinson’s disease treated with high cumulative doses of dopamine agonists. This year a meta-analysis reviewed nine studies comprising 639 prolactinoma patients treated with lower dose cabergoline and did not find any significant association of lower dose cabergoline with valvulopathy. This provides consider-
able reassurance to the clinician that medical manage-
ment of these uncommon but important pituitary lesions remains the cornerstone of treatment. Nonetheless, until definitive prospective data are available, it would be prudent to give prolactinoma patients advice as to cardiac symptoms that should be reported, and to discuss the option of monitoring their cardiovascular status either clinically or with serial echocardiography.

Acknowledgement
We would like to acknowledge Dr David Rogers (Ascot Radiology, Ascot Hospital) for assistance with radiology.

References
**Time and geographical variations in utilization of endocrine therapy for breast cancer in Australia**

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**Key words**
aromatase inhibitors, tamoxifen, breast cancer, drug use, Australia.

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**Abstract**

**Background:** Endocrine therapies, aromatase inhibitors and tamoxifen, are commonly used as an adjuvant treatment in women with breast cancer.

**Aims:** This study examined the trends in use of endocrine therapies in Australia between 1996 and 2008, including a comparison between Australian states.

**Methods:** Prescription and expenditure data for tamoxifen and aromatase inhibitors (1996–2008) were obtained from the Drug Utilisation Sub-Committee. We converted prescription data to defined daily doses (DDD)/1000 population/day, the international unit of drug utilization. Utilization data in each state/territory (2003–2008) were adjusted for female population and age-standardized incidence rates of breast cancer.

**Results:** Total utilization of endocrine therapies increased by 30% from 1.66 to 2.14 DDD/1000/day between 1996 and 2008. Over this period, there was a shift in use from tamoxifen to aromatase inhibitors which became the highest used products in 2008. Anastrozole was the most used aromatase inhibitor and its use increased markedly after being listed on Australia’s national Pharmaceutical Benefits Scheme (PBS) for early breast cancer in 2005 (average increase of 0.14 DDD/1000/day per annum between 2005 and 2008). PBS expenditure for endocrine therapies increased by 265% from $16 million to $58 million between 1996 and 2008. Utilization of endocrine therapies was overall comparable between regions except that it was substantially lower in the Northern Territory.

**Conclusions:** Use of aromatase inhibitors has overtaken use of tamoxifen in 2008. Further real-world effectiveness data are required to evaluate whether large associated increases in expenditures partly because of the higher costs of aromatase inhibitors are actually justified.

**Introduction**

Breast cancer is the most common cancer in Australian women. In 2006, breast cancer represented over a quarter (28%) of all reported cancer cases in women, with an age-standardized incidence of 112.4 per 100 000 population. Treatment of early breast cancer involves a range of therapies, including surgery, radiotherapy and chemotherapy. Additionally, endocrine adjuvant therapy is used to prevent the recurrence of breast cancer and prolong survival. For almost two decades, tamoxifen has been the standard endocrine treatment for postmenopausal women with oestrogen receptor-positive (ER+) invasive breast cancers. Tamoxifen is associated with a 41% relative reduction in the risk of recurrence and a 34% relative reduction in the risk of death in women with ER+/unknown tumours. During the last few years, a new class of medicines, the aromatase inhibitors, has been marketed for prevention of recurrence of breast cancer. The efficacy of these new drugs has been evaluated against tamoxifen in several randomized clinical trials, either as an upfront therapy instead of tamoxifen, in a sequential approach after 2–3 years of tamoxifen, or as an extended therapy following a 5-year course of tamoxifen. Compared with tamoxifen, aromatase inhibitors were shown to increase significantly disease-free survival and to have a different safety profile, including decreased risks of endometrial cancer and deep venous thrombosis and increased risks of arthralgia and fractures.

**Funding:** Dr C. Lu is supported by an Australian National Health and Medical Research Council Public Health Training Fellowship.

**Conflict of interest:** None.
In the late 1990s, the three aromatase inhibitors, anastrozole, letrozole and exemestane, were successively listed on the Australian Pharmaceutical Benefits Scheme (PBS), the national scheme which provides subsidized access to medicines for Australian residents, for treatment of advanced breast cancer. In July 2004, anastrozole was the first aromatase inhibitor to be listed for treatment of early breast cancer. It was initially restricted to women with a contraindication or intolerant to tamoxifen. Although this restriction was later removed in July 2005, there was still uncertainty about the effectiveness of the drug as no overall survival gain had been observed compared with tamoxifen. Concerns have been raised that the advantage of aromatase inhibitors over tamoxifen had been overemphasized and that tamoxifen might have been abandoned in clinical practice under the unproven assumption that aromatase inhibitors were prolonging life more than tamoxifen. The aim of this study was to examine the utilization of endocrine therapies for breast cancer in Australia, including geographical variations.

Methods

Monthly prescription and expenditure data for the period between January 1996 and December 2008 were obtained from the database maintained by the Drug Utilisation Sub-Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC database combines data on all subsidized prescriptions under the PBS and estimates of the number of non-subsidized prescriptions from a survey of community pharmacies. The drugs of interest (PBS item codes) were: anastrozole 1 mg (8179L), letrozole 2.5 mg (8245Y), exemestane 25 mg (8506Q), tamoxifen 10 mg (2109B), tamoxifen 20 mg (2110C) and toremifene 60 mg (8216K). Toremifene is of the same drug class as tamoxifen, selective oestrogen receptor modulators. We combined tamoxifen 10 mg and 20 mg data because the use of 10 mg tamoxifen was minimal during the study period (it accounted for 6.6% of all tamoxifen prescriptions in 1996 and only 1.9% in 2008).

Consumption data were expressed as defined daily doses (DDD)/1000 population/day. The DDD is based on the assumed average daily dose of a drug when used for its main indication in adults. It is the international standard recommended by the World Health Organization for drug utilization studies. The DDD/1000/day enables comparison of utilization regardless of different pack size, duration and dosage. We used DDD/1000 new breast cancer cases/day for each region to compare the utilization of endocrine therapies across states and territories between 2003 and 2008. Population statistics obtained from the Australian Bureau of Statistics and the 2005 age-standardized breast cancer incidence rates obtained from the Australian Institute of Health and Welfare were used to calculate the numbers of new female breast cancer cases for each region.

Results

Utilization in Australia

The total utilization of endocrine therapies increased by 28.9% from 1.66 DDD/1000/day in 1996 to 2.14 in 2008 (Fig. 1). Over the study period, there was a shift in use from tamoxifen to aromatase inhibitors. Utilization of tamoxifen increased from 1.66 DDD/1000/day in 1996 to a peak of 1.74 in 2001. Subsequently, its use showed a downward trend to 0.98 DDD/1000/day in 2008, a total decrease of 0.76 DDD/1000/day. Over the same period, the increase of 1.15 DDD/1000/day in use of aromatase inhibitors exceeded the reduction in tamoxifen utilization. The biggest change in use of endocrine therapies occurred in 2005, coinciding with the PBS listing of anastrozole for early breast cancer. Between 2002 and 2004, the average growth in use of aromatase inhibitors was 18.9% per annum, which increased substantially to 43.5% during 2005 and 2006. In 2008, the use of aromatase inhibitors became greater than the use of tamoxifen (54% versus 46% of the total use). The overall use of endocrine therapies was stable between 2002 and 2006 and then increased by 8% in 2007–2008.

Anastrozole was the most used aromatase inhibitor throughout the study period. Since it first became available under the PBS for the treatment of advanced breast cancer in March 1997, its use increased steadily but remained low (average increase of 0.02 DDD/1000/day per annum between 1997 and 2004) and increased at a higher rate after its PBS listing for early breast cancer in July 2004 (average increase of 0.14 DDD/1000/day per annum between 2005 and 2008). Similarly, utilization of letrozole increased at a higher rate following its listing for early breast cancer in July 2006. Use of exemestane and toremifene was low throughout the study period.

The PBS expenditure for endocrine therapies increased by 265% from $15 832 414 in 1996 to $57 789 247 in 2008 (Fig. 2). The reason is that the cost of aromatase inhibitors is around sixfold greater than that of tamoxifen per dispensing ($180.18 for 30 tablets of any of the aromatase inhibitors versus $60.24 for 60 tablets of tamoxifen). Between 1996 and 2004, the average expenditure growth was 9% per annum and increased to 16% per annum after the PBS listing change for anastrozole.
Utilization by region

The utilization of aromatase inhibitors increased while that of tamoxifen decreased in all states and territories continuously between 2003 and 2008. Throughout the period, the Northern Territory had the lowest utilization rates of endocrine therapies (1578.1 DDD/1000 new breast cancer cases/day in 2003 and 2025.0 in 2008), adjusting for female population and breast cancer incidence rates, and South Australia had the highest adjusted utilization rates (4127.2 in 2003 and 4287.3 in 2008). Differences between these regions reduced slightly from 2.6-fold in 2003 to 2.1 in 2008.

In 2008, Western Australia had the lowest proportion of use of aromatase inhibitors (50.0%) and the Australian Capital Territory had the highest proportion (59.8%). Tasmania had the highest use of both letrozole (22.8%) and exemestane (4.7%).

Discussion

Patterns of use of endocrine therapy in Australia have changed dramatically in recent years with tamoxifen gradually supplanted by aromatase inhibitors. Our findings are consistent with a study of 5486 women in the USA that found aromatase inhibitors became more frequently used than tamoxifen in 2002, just after the presentation of the preliminary results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial at the San Antonio Breast Cancer Symposium in December 2001. In Australia, the use of aromatase inhibitors began to increase significantly only after the PBS listing of anastrozole for early breast cancer in 2005. However, there was a small increase observed between 2001 and 2004, possibly because of the use of aromatase inhibitors in early breast cancer beyond the then PBS listing of aromatase inhibitors for advanced breast cancer. The overall use of endocrine therapies was on the whole stable between 2002 and 2006 and then increased by 8% in 2007–2008. This increase may be due to an increase in the breast cancer incidence in recent years, an increase in the proportion of women with breast cancer treated with endocrine therapies, and/or an increase in the persistence in use of endocrine therapies.

The utilization of endocrine therapies was markedly lower in the Northern Territory than other states/territories after adjusting for population and age-standardized breast cancer incidence. The Northern Territory had also slower rates of decline in tamoxifen utilization and uptake of aromatase inhibitors. There are
several possible reasons for the lower use of endocrine therapies in the Northern Territory observed in our study. First, the proportion of indigenous Australians is the highest in the Northern Territory among Australian jurisdictions (30.1% in 2006) and an important proportion of the population resides in remote or very remote areas. Although specialist cancer diagnosis and treatment services are available in this region, it is very likely that these are less accessed by indigenous Australians and people from remote areas. This lower use of preventative medicine is consistent with the observation of lower stage-adjusted survival rate for breast cancer among indigenous people compared with non-indigenous people. Second, the DUSC database does not capture use of medicines distributed through the Aboriginal Health Services under Section 100 of the National Health Act (1953). This may have led to an underestimation of the actual utilization in the Northern Territory. Differences observed between the regions in terms of choice and uptake of specific aromatase inhibitors possibly reflect prescriber preferences across Australia.

The PBS expenditure for endocrine therapies increased by 265% from 1996 to 2008, well above the 30% increase in use during the same period. In 2005, the PBAC considered that the use of anastrozole was cost-effective in women with early breast cancer based on the assumption that sufficiently large incremental survival benefits could be expected to justify the incremental costs. In 2008, the 100-month findings of the ATAC trial failed to confirm an improvement in overall survival. From a policy perspective, these results raise the important question of whether aromatase inhibitors at their current price remain a cost-effective alternative to tamoxifen. Aromatase inhibitors may still be prescribed because of the benefit in disease-free survival or to avoid adverse effects of tamoxifen. However, research showed no statistically significant difference between treatments in terms of quality of life in the ATAC trial at 5 years and the results were not more conclusive with other aromatase inhibitors. Empirical data did not find an improved adherence with anastrozole compared with tamoxifen, which could have inferred a better tolerance. It seems questionable that the differences in safety profiles, including decreased risks of endometrial cancer and deep venous thrombosis and increased risks of arthralgia and fractures with aromatase inhibitors compared with tamoxifen, could justify the significant increase observed in overall PBS expenditure. Currently, there are no systematic public processes for the PBAC to review either previous listing recommendations on the

Figure 2 Yearly Pharmaceutical Benefits Scheme (PBS) expenditure ($ millions) between 1996 and 2008. tamoxifen; anastrozole; toremifene; letrozole; exemestane; total.
basis of updated clinical or real-world effectiveness evidence or commission studies exploring the cost-effectiveness of alternative options, such as pharmacogenic testing.\textsuperscript{18} For example, women who are poor metabolisers of tamoxifen have worse outcomes and thus may gain real benefit from substituting tamoxifen with an aromatase inhibitor.\textsuperscript{19} Such studies are unlikely to be undertaken by pharmaceutical companies, in particular if medicines are off-patent like tamoxifen but could be conducted at a fraction of the current incremental expenditure on new medicines.

There are some limitations in this analysis that need to be acknowledged. First, we used aggregated data. A patient level analysis of breast cancer patients would be required to gain a more detailed understanding of the utilization patterns of these medicines over time, in particular the duration of treatment for either early or advanced breast cancer, use of aromatase inhibitors as an upfront therapy or in sequential use after tamoxifen, and the associated health outcomes. Second, although adjustments were made for breast cancer incidence rates in each region, the latest breast cancer incidence data available for this study were 2005 data.

**Conclusion**

Use of aromatase inhibitors has now overtaken tamoxifen. Further research is required to evaluate whether the consequent large increase in overall PBS expenditure has brought better quality of life and health outcomes for women with breast cancer. Such studies are critical if we want to achieve the best use of limited resources and truly improve health outcomes for all cancer patients.\textsuperscript{19}

**Acknowledgements**

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Intraperitoneal distribution imaging in ovarian cancer patients

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Abstract

Background/Aims: Optimal delivery of intraperitoneal (IP) chemotherapy is dependent on adequate drug distribution. An accurate understanding of the limitations of IP distribution is critical if we are to improve cytotoxic delivery through this route.

Methods: Using repeated scintigraphic peritoneography we investigated peritoneal fluid distribution in patients receiving IP therapy. Both early (1–6 h) and late (24–48 h) images were performed. The peritoneal cavity was divided into six regions; pouch of Douglas, left and right paracolic gutters, left and right subphrenic spaces and the right subhepatic space. The distribution in each region was classified as absent (0), faint (1) or intense (2). A total distribution score was calculated from the summation of distribution values for each of the six regions. Distribution was then graded according to the total distribution score as follows: Grade 0 = 0–3; Grade 1 = 4–6; Grade 2 = 7–9; and Grade 3 = 10–12.

Results: Twenty-six participants were included in the study: all 26 patients had early imaging performed and 21 of these also had late imaging. Thirteen (50%) and 15 (71%) patients had grade 1 or 2 IP distribution on early and late imaging respectively. The most common abdominal regions to show maldistribution were the subphrenic spaces.

Conclusions: This study highlights the deficiencies of distribution following IP drug delivery, with the majority of patients demonstrating multiple regions of faint or absent uptake on scintigraphic peritoneography imaging. Future large clinical studies investigating IP chemotherapy should include analyses of IP distribution to improve our understanding of optimal drug delivery through this route.

Introduction

The intraperitoneal (IP) delivery of antineoplastic agents as a management strategy for ovarian cancer has been explored for several decades. In ovarian cancer, the peritoneal cavity is the principal site of disease both at diagnosis and in patients at relapse. The delivery of chemotherapy directly into the peritoneal space has the potential to expose the cancer to higher concentrations of drug over sustained periods of time while minimizing systemic toxicity.

Multiple recent randomized phase III trials have now been reported using a combination of intravenous and IP chemotherapy for women with optimally debulked epithelial ovarian cancer.1–3 A National Cancer Institute (NCI) announcement was issued following the publication of the most recent large randomized trial.4 In this announcement it was concluded that a combination of IP and intravenous chemotherapy confers a significant survival benefit in women with optimally debulked disease, compared with intravenous chemotherapy alone. This conclusion has been supported by a recent meta-analysis, as well as a consensus statement from the 2006 International Consensus Conference on IP chemotherapy in Ovarian Cancer Patients.5,6 Although the subject of IP chemotherapy in ovarian cancer continues to engender considerable controversy, many clinicians have responded to these recent results and announcements by offering IP chemotherapy to this patient population.7,8

The pharmacokinetic principles that determine the suitability of chemotherapeutic agents for IP administration and the local complications related to IP therapy are well described.9–11 However, few studies have focused on the anatomical distribution of therapeutic agents delivered directly into the peritoneal cavity.12–17 IP distribution can be assessed by the IP injection of radioisotopes (scintigraphic peritoneography) or by instilling radiographic contrast media (contrast peritoneography).13 The radioisotope approach is preferable secondary to improved performance ease and greater safety.13 Using repeated scintigraphic peritoneography, we investigated peritoneal fluid distribution in patients intended for IP therapy.
Patients and methods

Data on IP distribution were obtained from patients at our institution undergoing repeated scintigraphic peritoneography through their enrolment in the MIDAS (Monoclonal Antibody Imaging and Dosimetry Assessment Study) or SMART studies between March 1999 and October 2002. The MIDAS study was a multinational single arm study designed to obtain data on the pharmacokinetics and biodistribution of IP therapy with Yttrium-90-Labeled HMFG1 murine monoclonal antibody (90Y-muHMFG1) by administering it concurrently with an IP imaging dose of 111Indium-labelled HMFG1. The SMART study was a multinational phase III study investigating the safety and efficacy of IP therapy with 90Y-muHMFG1, which has previously been reported.18

Patients entered onto the MIDAS and SMART studies were required to meet the following eligibility criteria: histologically proven epithelial ovarian cancer (International Federation of Gynaecology and Obstetrics stage Ic to IV) with evidence of a complete clinical response, following optimal surgical debulking and six cycles of platinum-based chemotherapy, as assessed by physical examination, computerized tomography (CT) scan and CA125. In addition, no evidence of macroscopic disease at a second-look laparotomy performed within 4–8 weeks of their final cycle of chemotherapy was required. All participants provided written informed consent prior to their enrolment. For eligible patients, temporary IP Tenckhoff catheters were inserted at the time of second look laparotomy. Following catheter insertion, 90Y-muHMFG1 was administered through the IP route with 1–1.5 L of normal saline. The target dose of 90Y-muHMFG1 delivered in each study was 666 MBq/m² and during the first hour after administration, the patient was moved frequently to ensure adequate dispersal of the infusate.

For the imaging studies, patients were rested supine. All imaging was performed on a dual-head gamma camera (Toshiba-7200, Toshiba Corp., Tokyo, Japan). In the SMART trial, <100 MBq 99m-Technetium sulphur colloid along with 500 mL normal saline infusion was administered through the peritoneal catheter using aseptic technique. Dynamic imaging of the anterior abdomen was obtained during infusion with 1 frame per minute until the 500 mL infusion was complete. The therapeutic dose of 90Y-muHMFG1 was then delivered in 1 L of normal saline. Thereafter, anterior and lateral static images were obtained at 1–6 h. Low-energy, high-resolution collimators were used. For the MIDAS trial, prior to the infusion, a transmission scan was performed using a flood source containing 185 MBq of 111Indium. Subsequently, 185 MBq 111Indium-HMFG1 was administered in combination with the therapeutic dose of 90Y-muHMFG1 in 1–1.5 L of normal saline. Because of the requirements for whole body dosimetry in this trial, acquisition included the entire body length (1024 × 256 matrix) using the 170 keV (20%) and 245 keV (17%) energy windows of the 111Indium emission spectrum. Medium-energy, high-resolution collimators were used. Following IP administration both early (1–6 h) and late (24–48 h) whole body imaging was performed.

The peritoneal cavity was divided into six anatomic regions to define accurately the extent of IP distribution; pouch of Douglas, left and right paracolic gutters, left and right subphrenic spaces and the right subhepatic space. In each region, for early and late imaging, the degree of IP distribution was classified as absent (0), faint (1) or intense (2). A total distribution score was calculated from the summation of distribution values for each of the six regions, with a maximum score of 12 representing intense distribution in all regions. The extent of IP distribution was then graded according to the total distribution score, using the following scale: Grade 0 = 0–3; Grade 1 = 4–6; Grade 2 = 7–9; and Grade 3 = 10–12. A senior nuclear medicine physician performed the scoring of all images.

Results

IP distribution imaging was available for 26 patients in total; 15 patients enrolled in the MIDAS study and 11 patients in the SMART study. Early images were obtained for all 26 patients; however, only 21 patients had corresponding late images for comparison.

The grading of IP distribution on early (n = 26) and late (n = 21) scintigraphic peritoneography images is shown in Table 1. No patients had grade 0 IP distribution. Thirteen (50%) and 15 (71%) patients had grade 1 or 2 IP distribution on early and late imaging respectively. Thirteen (50%) and six (29%) patients had grade 3 IP distribution on early and late imaging. When comparing alterations in IP distribution between early and late images, 2 patients (10%) showed no change in distribution, 16 patients (76%) showed deterioration in distribution and 3 patients (14%) an improvement in distribution over time. In 14 patients (66%) the late imaging, compared with early imaging, showed a dependent pattern with more tracer accumulating in the pouch of Douglas and paracolic gutters than in the subphrenic spaces (Fig. 1).

The most common abdominal regions to show inadequate distribution were the subphrenic spaces. Of all regions on imaging showing faint or absent uptake, 24% showed maldistribution in the right subhepatic space, 23% in the left subhepatic space, 19% in the right subhepatic space, 17% in the left paracolic gutter, 10% in the right paracolic gutter and 9% in the pouch of Douglas. Of those images showing faint or absent uptake in the
subphrenic spaces, 41% were on early imaging and 59% on late imaging, highlighting the dependent changes noted over time.

In total, 11 of 26 patients (42%) were found to have a leak from the IP catheter: 9 had evidence of extra-abdominal leakage, 1 had evidence of pleural leakage and 1 had leakage at both extra-abdominal and pleural sites (Fig. 1). Of these 11 patients, 6 (55%) and 9 (82%) had grade 1 or 2 distribution on early and late imaging respectively.

### Table 1 Grading of IP distribution on scintigraphic peritoneography

<table>
<thead>
<tr>
<th>Grade</th>
<th>Distribution</th>
<th>Early imaging†</th>
<th>Late imaging†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total distribution score‡</td>
<td>n = 26 (%)</td>
<td>n = 21 (%)</td>
</tr>
<tr>
<td>Grade 0</td>
<td>0–3</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Grade 1</td>
<td>4–6</td>
<td>1 (4%)</td>
<td>5 (24%)</td>
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<tr>
<td>Grade 2</td>
<td>7–9</td>
<td>12 (46%)</td>
<td>10 (47%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>10–12</td>
<td>13 (50%)</td>
<td>6 (29%)</td>
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</table>

†Early imaging (1–6 h), late imaging (24–48 h). ‡Total distribution score: calculated from the summation of the distribution values assigned to each of the six anatomic regions: absent (0), faint (1), intense (2).

### Discussion

Optimizing exposure of serosal surfaces to the drug-containing infusate is critical to the success of IP chemotherapy and radioimmunotherapy. This study highlights the deficiencies of distribution following IP drug delivery, with the majority of patients demonstrating multiple regions of faint or absent uptake on scintigraphic peritoneography imaging. Importantly, this study was performed in patients with no evidence of macroscopic

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![Figure 1](image-url)  
*Figure 1 Scintigraphic peritoneography images. (A) Early image showing intense uptake in all six abdominal regions (Grade 3). (B) Corresponding late image at 24 h showing faint uptake in the right and left subphrenic regions (1) and intense uptake in all other abdominal regions (Grade 3). (C) Early image showing extra-abdominal leakage (1), intense uptake in the pouch of Douglas (2) and faint uptake in all other abdominal regions (Grade 2). (D) Corresponding late image at 24 h showing extensive extra-abdominal leakage.*
disease at the time of second-look laparotomy and in whom, in the opinion of the surgeon, no adhesions were present to obstruct distribution.

There are limited published data on the rate of maldistribution with IP therapy and there is considerable variation between studies. Using serial scintigraphic peritoneography, early studies suggested high rates of maldistribution (up to 70%), even in patients without residual disease. Three recent trials have assessed baseline distribution prior to IP treatment in patients with no residual macroscopic disease and identified maldistribution rates of only 1–15%. The criteria for assessment of inadequate distribution in these studies were not defined. No standardized radiological criteria for assessing IP distribution exist, making interpretation difficult. Our study analysed the IP distribution of a monoclonal antibody and the results may not generalize to those patients receiving IP chemotherapy because of differences in pharmacokinetics. However, the high rate of maldistribution identified highlights the need for a standardized approach to the assessment and evaluation of IP distribution in future prospective trials.

Previous contrast studies have suggested that the subdiaphragmatic spaces are the regions most likely to show maldistribution, as demonstrated in our study. However, serial studies have not identified a uniform pattern, with some patients showing worsening and others improvement in the distribution over time. In addition, the correlation between maldistribution and clinical outcome is currently not well understood. This remains an important consideration, which has not been addressed in large clinical trials. An accurate understanding of the limitations of IP distribution using current techniques is critical if we are to improve cytotoxic delivery through this route.

Leakage from the IP catheter was a common occurrence in our study. A recent report of 17 patients also enrolled in the MIDAS study, similarly confirmed a high rate of extraperitoneal leakage at 24%. Although IP distribution was not reported in this analysis, it was demonstrated that leakage was associated with lower blood radioactivity levels of $^{111}$Indium-labelled HMFG1. The extent to which extraperitoneal leakage contributes to maldistribution and the degree to which this compromises therapeutic effectiveness remain unknown.

It is possible that the IP distribution of cytotoxic agents may be enhanced through attention to the important technical aspects of the procedure. The original Tenckhoff peritoneal dialysis catheters used in this study have a number of important limitations when used for IP chemotherapy. In particular, they have a Dacron cuff, which requires fixation to the abdominal wall to prevent catheter movement and leakage along the track. The use of a single-lumen venous-access catheter attached to an implanted subcutaneous port has now been reported to be superior to the Tenckhoff catheter design, and has superseded its use in clinical practice. However, further studies are needed to understand the impact of catheter placement techniques and the timing of catheter insertion in relation to primary surgery, on subsequent IP distribution.

In addition, no studies comparing different techniques of administration of chemotherapy in this patient population have been performed. Previous studies of peritoneal dialysis techniques have concluded that dialysate volumes and patient position both impact on the effectiveness of peritoneal exchange. During IP drug administration, it therefore appears important to optimize the volume in which the drug is delivered and to consider patient position as an important determinant of drug distribution. In the case of IP chemotherapy, the optimal volume of infusate is not known. A large volume of fluid is generally infused in an attempt to ensure that the drug-containing solution reaches all IP surfaces. Tilting the patient head down after the infusion appears to be advantageous; however, the optimal duration for this positioning is unknown. In addition, after the infusion patients are encouraged to change position at 15 min intervals for 2 h to enhance intra-abdominal distribution. Limitations in both the volume of infusate and patient positioning may have hampered adequate IP distribution in our study. Furthermore, in the SMART study, differences in the volume of infusate used for the imaging studies and the volume of infusate used for delivery of the therapeutic dose may have led to differences in distribution. However, to date, adequate investigations into these clinical approaches have not been performed in order to define the impact they have on IP distribution.

Our study was done in patients with no macroscopic disease who had received six cycles of intravenous chemotherapy, but had not been exposed to IP chemotherapy. In the most recent randomized trial, six cycles of IP chemotherapy with both cisplatin and paclitaxel were planned in patients who had residual macroscopic tumour up to 1 cm. It is not known whether IP distribution may deteriorate with progressive cycles of IP chemotherapy. Serial studies of IP distribution after multiple cycles of IP chemotherapy are needed to address this issue. The results of such studies may help determine the optimal number of IP cycles to administer, and assist in designing less toxic regimens with fewer cycles of IP chemotherapy that could then be tested in randomized trials.

**Conclusion**

If the tumour surface is inadequately exposed to the drug-containing infusate then the rationale behind the
regional administration of chemotherapy is challenged. Conceptually, residual peritoneal disease may contribute to maldistribution and therefore limit the delivery of chemotherapy precisely to where it is most needed. Studies aimed at improving IP distribution should receive a high priority because it is possible that much of the residual tumour burden is untreated or under-treated by conventional approaches. Future large clinical studies incorporating IP chemotherapy into treatment regimens should include analyses of IP distribution in order to enhance our understanding and enable us to optimize drug delivery through this route.

References


Randomized cross-over trial comparing inpatient and outpatient administration of high-dose cisplatin

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Key words
Cisplatin, outpatient, inpatient, patient preference, health services.

Abstract

Background/Aims: Treatment with high-dose cisplatin (HDC) previously required inpatient (IP) admission with overnight hospitalization, but recently practice has shifted to outpatient (OP) therapy. We aimed to determine whether it is preferable to give HDC as an IP or OP using a two-period cross-over trial.

Methods: Eligible patients were starting chemotherapy with ≥2 cycles of HDC (≥100 mg/dose) and were suitable for OP treatment. All patients received an IP cycle and OP cycle: the order was randomly allocated. Pre-hydration, anti-emetics and chemotherapy were identical for IP and OP. Post-hydration varied by group (3 L normal saline (NS) for IP, 2 L NS for OP). The primary outcome was patient preference for IP versus OP treatment. Secondary outcomes included aspects of health-related quality of life, adverse events (dose delays and reductions, elevated creatinine and unplanned readmissions) and resource use.

Results: Fifty-nine patients were randomized, 53 completed two cycles of HDC. Most patients preferred OP treatment (36 vs 13, P = 0.002). There were no significant differences in patients’ ratings of nausea, vomiting, fatigue, anxiety, depression or overall quality of life. Adverse events were few and unrelated to IP versus OP treatment. Nursing time was longer for IP than OP (163 vs 104 min, P < 0.001).

Conclusion: OP treatment was preferred by most patients, appeared safe and used less resources.

Introduction

High-dose cisplatin (HDC) chemotherapy is the backbone of chemotherapy regimens for a wide variety of malignancies, including many given with curative intent. HDC is highly emetogenic and potentially nephrotoxic; optimal administration requires effective anti-emetic therapy and vigorous hydration. Patients receiving HDC have traditionally been admitted to hospital as inpatients (IP) for at least one night to deliver successfully these supportive treatments.

The last 20 years have seen a major shift in the administration of cytotoxic chemotherapy from IP to outpatient (OP) settings. Advances in anti-emetic therapy, improved understanding of risk factors for nephrotoxicity and experience with OP administration of multiple-day low-dose cisplatin has made OP administration of single day HDC feasible. Indeed, many Australian and American chemotherapy centres have adopted OP treatment as routine for suitable patients having HDC. In Europe and the UK, there is a mix of both IP and OP administration in clinical practice.

Calls for well-designed trials examining the impact of OP chemotherapy on both patients and hospitals were first made 15 years ago, and have remained largely unanswered despite the shift in practice. Current reports are either small, retrospective, or describe therapy with superseded supportive care protocols. Prospective information on patients’ experience of OP HDC can be found in more recent trials of chemotherapy and anti-emetics, but these contain no comparison of IP versus OP treatment. We were unable to find any reports of randomized controlled trials comparing the IP and OP administration of HDC.

OP HDC therapy might improve patients’ psychological well-being by removing the anxiety and dislocation associated with overnight hospitalization, and diminishing self-perceptions of ‘sickness’. In addition, OP treatment is also likely to impose fewer burdens upon hospitals and be cheaper, as long as it is not associated with a higher incidence of adverse events. Conversely, it is possible that reduced accessibility to healthcare staff in the acute
post-treatment period might result in more emergency presentations to hospital because of uncontrolled toxicity (e.g. emesis) and that patients might feel unsupported in the home environment. As lesser volumes of post-cisplatin hydration are often prescribed for OP versus IP treatment, it is also possible that there is a greater risk of nephrotoxicity with OP therapy.

We conducted a prospective, randomized cross-over trial with the primary objective of comparing administration of HDC as an IP versus an OP. In particular we assessed patients’ preferences, health-related quality of life (HRQL), adverse events and hospital resource use.

Materials and methods

The target population was patients commencing a chemotherapy regimen including cisplatin administered as a single daily dose of 100 mg or more for at least two cycles. All patients were recruited from the oncology clinics of the Sydney Cancer Centre. Patients were 18 years of age or older, had normal renal and hepatic function, an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, and must have been judged suitable by their physician to be treated as an OP (i.e. adequate support at home). Adequate support at home was defined by (i) each patient either lived with another person or had a home telephone with which they could easily contact a nominated contact person; (ii) each patient showed means to organize their own transportation to hospital in case of an emergency (e.g. the ability to call an ambulance); (iii) each patient was independent with their activities of daily living.

Exclusion criteria included previous treatment with cisplatin, a history of renal impairment or symptomatic heart failure, and pregnancy or lactation. All patients provided written informed consent and the protocol was approved by local ethics review committees at all participating sites.

The study design was a randomized, unblinded, two-period cross-over trial. Participants were scheduled for one cycle of IP HDC and one cycle of OP HDC 21 days apart. The order of administration (IP first or OP first) was allocated using a computerized program that dynamically balanced randomization for the cisplatin-containing chemotherapy regimen. Participation in the study was for the duration of the first two cycles of chemotherapy, which extended up to the day of assessment 3–4 weeks after the second cycle of treatment.

Both IP and OP regimens included pre-hydration with 1 L of normal saline (NS) over 1 h followed by 100 mL of intravenous 20% mannitol, before the cisplatin which was given in 1 L of NS over 2 h. Following the cisplatin, the OP treatment comprised 2 L of NS over 6 h, and discharge that evening with anti-emetic medication and a follow-up telephone call the next morning. The IP treatment comprised 3 L of NS over 18 h with discharge the following morning. Anti-emetics included routine dexamethasone and tropisetron.

The primary outcome was patient preference for IP versus OP treatment. Secondary outcomes included aspects of HRQL, adverse events (hospital readmissions, elevated creatinine), the ability to deliver full doses of chemotherapy in subsequent cycles (dose delays, dose reductions), and resource use (days spent in hospital, time spent with healthcare staff).

Patient preference for IP or OP treatment was measured at a planned assessment 3–4 weeks after the second cycle using a 7-point preference scale. This scale asked patients to identify whether they preferred IP, OP or had no preference. If they preferred IP or OP, they were asked to indicate whether it was ‘much better’, ‘moderately better’ or ‘a little better’. All patients completed baseline assessments of HRQL with the (i) Global Quality of Life (GLQ)-8, including eight linear analogue self-assessment scales for anxiety/depression, feeling sick, numbness/pins and needles, hair loss, tiredness, appetite/taste, sexual interest and ability, and thought of chemotherapy; (ii) GLQ-uniscale (a single linear analogue self-assessment scale rating overall quality of life) and (iii) Utility-Based Questionnaire-Cancer (UBQ-C), including 23 items assessing physical ability, social/usual activities, distresses and overall quality of life. The UBQ-C was also completed on day 1 of cycle 2 and 3–4 weeks after cycle 2. The GLQ-8 and GLQ-uniscale were completed at the same time points as well as on day 7 of cycles 1 and 2. Serum creatinine was measured on day 1 of each cycle and 3 weeks after cycle 2. Medical and nursing staff recorded the number of encounters they had with patients, the time spent at each encounter, and time spent on performing associated tests and procedures.

The signed rank sum test was used for assessment of the patient preferences. This is a non-parametric test for location. Patients who specified no preference were given a score of zero. Patients who preferred IP treatment a little better, moderately better or much better were assigned scores of −1, −2 or −3 respectively; patients who preferred OP treatment a little better, moderately better or much better were assigned scores of 1, 2 or 3 respectively. The signed rank sum test was used to test the null hypothesis that the distribution was centred around 0. Fisher’s exact test was used to examine associations between patient characteristics and treatment preference. The $\chi^2$ test for equal proportions was used to compare the number of patients preferring their third cycle as an IP versus an OP.

Cross-over analysis for continuous outcomes was conducted as per the method of Hills and Armitage, using
analysis of variance to examine for treatment, period and order effects. This analysis was conducted for aspects of quality of life, serum creatinine, number of days required in hospital, numbers of visits, and total time with medical staff. The Mainland–Gart test was used to conduct cross-over analyses for binary outcomes. The conditional binomial test was used to test for associations between treatment regimen (IP or OP) and delay of subsequent cycles.

The planned sample size of 60 subjects was designed to provide >80% power with a two-sided type 1 error rate of 5% to detect differences of 0.75 on the 7-point preferences scale (estimated standard deviation 2), and of 1 on the 0–10 scales for aspects of quality of life (estimated standard deviation 2.5). Recruitment was stopped early because of slow accrual before analysing or examining the results.

Results

One hundred and forty-three patients were screened for eligibility and 59 were randomized. Fifty-three were eligible for the final analysis (Fig. 1). Table 1 shows the baseline characteristics of the 53 patients, which were well matched between the two groups. The majority of patients in the study were men, and lung cancer was the commonest tumour. There were more patients with gastric cancer in the IP-first group (eight vs two cases).

Treatment preferences

More patients preferred treatment as an OP than as an IP (36 vs 13, \( P = 0.002 \), three patients had no preference, one died after cycle 2 before assessment). The majority of patients rated OP treatment ‘much better’ (31%)
or ‘moderately better’ (29%) (Fig. 2). Asked how they would prefer to have their third cycle of HDC, 40 patients indicated as an OP versus 12 who indicated as an IP ($P < 0.001$). Patient preference for IP versus OP treatment did not vary by randomization to IP or OP first, nor by age, gender, ECOG performance status, tumour type, or chemotherapy regimen (Table 2).

### Health-related quality of life

Complete data for the GLQ-8 and GLQ-uniscale were available for 51 of the 53 patients for days 1 and 7 of cycles 1 and 2, and for 40 patients at the assessment point 3–4 weeks after cycle 2. As assessed on the GLQ-8, there were no significant differences between groups in patients’ ratings of anxiety/depression, sickness, numbness or pins and needles, loss of hair, tiredness, appetite or taste disturbance, sexual interest or ability, or thoughts of having chemotherapy. There was also no significant difference in ratings of overall quality of life on the GLQ-uniscale (Fig. 3). Data for the UBQ-C were available for 52 patients on day 1 of cycle 2, but only 38 completed the questionnaire 3–4 weeks after cycle 2. The only significant effect of IP versus OP treatment on HRQL was that patients rated the ‘thought of chemotherapy’ as significantly more distressing 3 weeks after treatment as an IP than as an OP (treatment effect, $P = 0.035$).

Significant period effects were noted for ‘loss of hair’ ($P < 0.001$), ‘sexual interest or ability’ ($P = 0.014$) and ‘your

### Table 1  Baseline characteristics. Numbers are n (%), unless otherwise specified

<table>
<thead>
<tr>
<th></th>
<th>Inpatient first (n = 27)</th>
<th>Outpatient first (n = 26)</th>
<th>Overall (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (Q1, Q3)</td>
<td>57 (42, 63)</td>
<td>54 (45, 59)</td>
<td>56 (45, 62)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (85)</td>
<td>18 (69)</td>
<td>41 (77)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (15)</td>
<td>8 (31)</td>
<td>12 (23)</td>
</tr>
<tr>
<td>Median creatinine, μmol/L (Q1, Q3)</td>
<td>77 (70, 86)</td>
<td>75 (71, 84)</td>
<td>75 (71, 85)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>23 (85)</td>
<td>23 (88)</td>
<td>46 (87)</td>
</tr>
<tr>
<td>1</td>
<td>3 (11)</td>
<td>3 (12)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>2</td>
<td>1 (4)</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Type of cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>8 (30)</td>
<td>10 (38)</td>
<td>18 (34)</td>
</tr>
<tr>
<td>Gastric</td>
<td>8 (30)</td>
<td>2 (8)</td>
<td>10 (19)</td>
</tr>
<tr>
<td>Bladder</td>
<td>2 (7)</td>
<td>2 (8)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (33)</td>
<td>12 (46)</td>
<td>21 (40)</td>
</tr>
<tr>
<td>Chemotherapy regimen (cisplatin dose, mg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECF (60 mg/m²)</td>
<td>11 (41)</td>
<td>6 (23)</td>
<td>17 (32)</td>
</tr>
<tr>
<td>Cisplatin/vinorelbine (100 mg/m²)</td>
<td>6 (22)</td>
<td>6 (23)</td>
<td>12 (23)</td>
</tr>
<tr>
<td>Cisplatin alone (100 mg/m²)</td>
<td>0</td>
<td>3 (12)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>CMV (70 mg/m²)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Other†</td>
<td>9 (33)</td>
<td>10 (38)</td>
<td>19 (36)</td>
</tr>
<tr>
<td>General health last 3–4 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>2 (8)</td>
<td>2 (8)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Very good</td>
<td>7 (27)</td>
<td>9 (34)</td>
<td>16 (31)</td>
</tr>
<tr>
<td>Good</td>
<td>7 (27)</td>
<td>7 (27)</td>
<td>14 (27)</td>
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<tr>
<td>Fair</td>
<td>8 (30)</td>
<td>8 (31)</td>
<td>16 (31)</td>
</tr>
<tr>
<td>Poor</td>
<td>2 (8)</td>
<td>0</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

†Patients all received over 60 mg/m² cisplatin. CMV, Cisplatin, methotrexate, vinblastine; ECF, epirubicin, cisplatin, 5-fluorouracil; ECOG, Eastern Cooperative Oncology Group.

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![Figure 2](image-url)  
**Figure 2** Histogram for treatment preferences question.
health state today’ ($P = 0.019$), with ratings after cycle 2 being consistently worse than after cycle 1, regardless of whether treatment was as an IP or OP first. There were no significant order effects.

**Adverse events**

There were nine unplanned hospital admissions after the 53 IP chemotherapy cycles and seven after the 53 OP cycles ($P = 0.428$). Fever, infection and vomiting were the most common reasons for unplanned admissions and were equally common after IP and OP chemotherapy. One patient died from progressive malignancy during an unplanned admission (after cycle 2 of chemotherapy, given as an OP). There were no significant treatment, period or order effects for serum creatinine values.

**Ability to deliver subsequent cycles of chemotherapy**

There was no significant difference in the frequency of subsequent chemotherapy delays after treatment as an IP versus as an OP. Only one patient had a prescribed dose reduction of cisplatin for their next cycle of treatment (dose reduction for cycle 2 after cycle 1 was given as an IP).

**Resource use**

The mean length of time spent in the hospital for the administration of an IP chemotherapy cycle was 2.1 days (a hospital admission with discharge the following day was recorded as a 2-day length of stay). The mean length
of stay for all OP cycles was 1 day. Combining unplanned hospital admissions and chemotherapy administration, the mean time in hospital per patient was 3.0 days for IP treatment versus 1.8 days for OP treatment ($P = 0.007$).

Data for staff interaction with patients were available on 52 of 53 patients. A nurse saw all patients during chemotherapy delivery. The mean number of encounters between nurse and patient was 5.0 per IP cycle and 3.6 per OP cycle ($P < 0.001$). The mean time spent by nurses attending to patient care per cycle was significantly greater for treatment as an IP than as an OP (163 vs 104 min, $P < 0.001$). Doctors saw patients during chemotherapy administration in 37 of 53 cycles (71%) given as an IP and 4 of 53 cycles (8%) given as an OP ($P < 0.001$).

**Discussion**

Most patients in this study preferred having their HDC as OP rather than as an IP. The magnitude of the effect was large and clinically significant, with 60% of patients indicating OP treatment was ‘much better’ or ‘moderately better’. Patients’ preferences for OP versus IP administration of HDC have not been reported previously, although high rates of patient satisfaction with OP chemotherapy have been observed. Patients found the thought of chemotherapy more distressing after having it as an IP than as an OP. However, overall quality of life and other specific aspects of HRQL were not affected by whether HDC was given as an IP or as an OP.

Treatment as an OP was not associated with an increase in unplanned hospital readmissions or nephrotoxicity. A recently reported case series supports our observation that HDC can be safely administered with minimal risk of nephrotoxicity. A retrospective review of 400 patients also suggested that toxicity from IP and OP HDC is comparable. Similarly, a previous review of anti-emetic trials suggests that nausea and vomiting induced by chemotherapy (not only cisplatin) is not affected by whether chemotherapy is given as an OP or as an IP.

Fewer hours were spent in hospital when receiving treatment as an OP than as an IP, as expected. This benefit was maintained when additional unplanned admissions were also considered (chemotherapy time + unplanned readmissions). In addition, treatment as an OP resulted in fewer staff encounters and less nursing time than treatment as an IP. In Australia, all patients are routinely seen in an oncology clinic before each cycle of HDC, so the difference in medical officer visits is real and not attributable to differing times of medical review (i.e. IP reviewed during chemotherapy, OP reviewed in clinic). Shorter hospital stays and fewer total days in hospital should result in lower costs. A small, randomized trial of 22 patients found modest savings when administering infusional 5-fluorouracil over 5 days as an OP. Similar results were obtained on a larger scale in a retrospective analysis of patients receiving cisplatin and 5-fluorouracil for cervical cancer, but the patients assessed were receiving concurrent radiotherapy which would affect the treatment logistics, complications and hence costs.

The main strengths of our study are its prospective nature and cross-over design, which allow each subject’s response to IP treatment to be contrasted with his or her response to OP treatment. The cross-over design is useful to determine patient preferences in situations where treatment affects quality of life. The presence of a treatment effect in the absence of any period or order effect supports our choice of a cross-over design and the adequacy of a 3-week interval between treatment cycles. The main limitation of our study is its small sample size. However, the efficiency of the cross-over design provided adequate power to detect a significant difference in preferences, and to exclude any significantly adverse effects on quality of life. It should also be noted ensuring adequate intake of fluid and electrolytes is important for minimizing the nephrotoxicity caused by cisplatin, especially for those living in hot and humid climates where insensible losses are substantial. Additional pre- and posthydration intravenous fluids may be required for those unable to drink sufficient fluids.

OP administration of HDC has become common practice in many centres since we completed this study. The reduced strain on hospital resources and IP beds is important to overburdened hospitals and healthcare systems. However, the most compelling argument for administering HDC as an OP is that most patients preferred it. Patient selection for OP treatment is important, and some patients may be better suited to treatment as an IP, for example those with limited support. We have shown that most patients who had adequate social support and reasonable performance status preferred to have HDC as an OP, and recommend it be offered to all such patients.

**References**


Benchmarking opioids in the last 24 hours of life

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Key words
benchmarking, analgesics opioid, hospice, clinical governance.

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Abstract
Background/Aims: Opioid dosages are titrated against symptoms with large variations between patients. For self-assessment of prescribing, and for clinical governance, it is important to know the normal prescribing patterns across New Zealand (NZ). The aims of this study were to document opioids and dosages given to patients in the last 24 h of life to identify normal practice and allow prescribers to reflect on their own practice.

Methods: A cross-sectional benchmarking design with retrospective chart review was carried out among 14 NZ hospices. Data \((n = 352)\) on opioid dosages were analysed for inter-hospice variability (ANOVA). Parenteral morphine equivalent daily dose was used to analyse the dosage of different opioids.

Results: Overall, 95% of dying patients received an opioid. Of these 71% received morphine, 17% fentanyl, 10% methadone 9.5% oxycodone. The dosages delivered are conservative compared with international data, with a geometric mean of 47.8 mg. There was no significant difference in mean dosages of opioids prescribed between hospice teams. There was, however, a significant difference between the dosage of opioid for those on the Liverpool Care Pathway for the Care of the Dying and those who were not (63.1–44.4 mg), and between those with malignant and non-malignant disease (53.8–26.0 mg). Opioid footprints show different hospices have different patterns of opioid use.

Conclusion: The parameters of what normal opioid prescribing is in the last days of life in NZ can be described from these data. There is value in repeating this exercise both for clinical governance and for professional reflection and self-assessment.

Introduction

For the physician caring for a dying patient, or for the involved institution, it is not currently possible to determine whether an opioid prescription is in keeping with that of other New Zealand (NZ) prescribers and institutions. It is not unusual for doctors to be delivering care in relatively isolated contexts without the security of a collegial team with whom they compare practice. Nor is it not unheard of for doctors to be criticized for the dosages they prescribe.\(^1\)\(^-\)\(^4\) ‘Normal’ prescribing in NZ is not well documented.

Best practice for pain relief has been defined in terms of screening, assessment, education, availability of breakthrough medication, bowel regimens and follow up.\(^5\)\(^-\)\(^6\) Morphine remains the World Health Organization-endorsed gold standard opioid, and in most situations is considered the opioid of first choice\(^6\)\(^-\)\(^10\) because of its ‘versatility, clinical experience, and non-inferiority to other potent opioids’.\(^7\) Despite these recommendations, in some countries other opioids are overtaking morphine as first-line strong analgesia.\(^11\)\(^-\)\(^12\)

For patients at the end of life with pain and dyspnoea, opioids are titrated against symptoms, and not to specified dosage levels. Titration is based on a clinical assessment and goals derived from discussion with the patient, their family, caregivers and colleagues.\(^11\) There is no pre-defined ‘correct dose’, and while some cancer patients require no opioids, others require several grams of morphine for good symptom relief.\(^12\)\(^-\)\(^14\) Average opioid dosage varies between countries.\(^12\) There is the suggestion that opioid dosage has been decreasing in some units, but the literature is not conclusive.\(^15\)\(^-\)\(^16\) Concern that higher or escalating dosage is associated with hastened death has been shown to be unfounded.\(^13\)\(^-\)\(^17\)\(^-\)\(^19\) It has been suggested that change of opioid dosage leading up to death can be a useful clinical indicator and benchmark.\(^1,13\) Recording the opioid dose in the final 24 h of life has the advantage of simplicity and compliance over multiple benchmarking sites.

For NZ practitioners, morphine and methadone have been the mainstays of opioid management. More recently, the choice of opioids has increased, with the funding of fentanyl transdermal patches in 2004,\(^20\) and oxycodone...
in a variety of preparations in 2005. Along with an increased range of available opioids, there are advocates for combining opioids to achieve analgesic synergies, giving rise to further permutations in prescribing.

Different countries have their own particular constellation of funded and unfunded medications, and configuration of palliative care services. There are 18 hospices with inpatient beds in NZ, ranging in size from a two-bed unit in a rural area, up to an 18-bed unit in the city. Each hospice has developed independently according to community need and input. Each has access to specialist advice, but it has not been possible to recruit specialist staff to all units, particularly away from the bigger city centres. There is a real possibility of isolation for some practitioners who are unable to get together regularly with peers to compare and share their work.

Current best practice guidelines are flexible when it comes to prescribing opioids and dosages. This allows for the prescriber to deal with the unique situation each patient brings in the context of their specific health system. Such flexibility though must not obscure that prescribers must be cognisant of ongoing changes in analgesic management and prescribing options. It is important for physicians and those responsible for clinical governance to know that, given the possibility for idiosyncratic prescribing, they are working within the boundaries of acceptable practice set by their colleagues.

Study purpose
The purpose of this benchmarking study was to provide information to reassure NZ practitioners that they are prescribing in a manner consistent with colleagues. To this end the quantities and range of opioids being received by patients under hospice care around NZ in the last 24 h of life were assessed. This window of time was chosen because the dosage given in the last few days of life is generally indicative of the dosage given up to that time, and there are published reports of medication use in the last 24 h. Our aim was to describe normal prescribing practice in NZ and the degree of variation between centres.

Method
We utilized a cross-sectional design with retrospective chart review.

Sample and recruitment
All hospices with inpatient beds identified through the Hospice New Zealand website were invited to take part. An open invitation was circulated through the Hospice New Zealand email list, and written invitations sent to the identified hospices. The invitation included a document outlining the aims of the study and instructions on how to complete the electronic data collection template.

Procedure and study variables
Hospices were asked to undertake a retrospective review of notes and drug charts of consecutive patients who died under their care in February and March 2008. The expectation was that this would provide at least 20 patients for each unit, recognizing some small hospices would not meet this goal, and larger hospices would exceed it. For admission to the study, patients had to be under hospice care for at least the last 24 h of their life, and be 18 years or older. An accurate record of medications administered had to be available, which for many hospice teams confined the suitable patient pool to patients who had died in their inpatient unit (IPU).

The study variables were age, gender, diagnosis (coded using the UK palliative care minimum data set with the addition of melanoma as a specific diagnosis), use of the Liverpool Care Pathway (LCP), and place of death (coded as either IPU, private hospital, public hospital or home).

The template allowed for documentation of each opioid used, the routes of administration, and the total amount of medication administered in the 24 h before death. For continuous subcutaneous medication or long-acting medication which was either started or changed during the last 24 h, pro-rata calculation was used to ascertain the actual dosage delivered. Other medications given for symptom management and any comments thought to be relevant were also recorded.

The authors collated the templates, and the initial analysis was shared with the contributing hospices for comment and correction before a final analysis was carried out.

Analysis
Data were anonymized by allocating each hospice a number, and entered into SPSS (Version 16.0; SPSS, Chicago, IL, USA) for statistical analyses.

To illustrate the range and relative frequencies of opioid use for each hospice, the concept of an ‘opioid footprint’ was conceived. This is a visual tool that presents information as a bar graph, showing the range and relative frequency of opioids used. It is derived by noting for each patient which opioids were administered within the time window. Only the fact of administration is counted, not the frequency for each patient. Thus, a patient may have received morphine in a continuous
subcutaneous infusion, extra morphine as subcutaneous ‘breakthrough’ analgesia, plus fentanyl as a single subcutaneous breakthrough medication. This patient would contribute a single count for morphine and a single count for fentanyl towards the hospice opioid footprint. By aggregating all the counts for each hospice, and expressing the opioid counts as a percentage of all counts, a bar graph was generated.

The Edmonton method was used to derive a single figure to allow for a comparison of the dosage of different opioids. This method converts opioid dosages to a parenteral morphine equivalent daily dose (pMEDD) using a published conversion table.28 A conversion factor of 20 was used for alfentanil.29

A logarithmic transformation was done on the combined opioid dosages to approximate a normal distribution, generating a geometric mean. Without this transformation, the distribution of opioid dosage is positively skewed and parametric analysis was not possible in comparing benchmarking sites.30

Ethics

A certificate of approval was obtained from the New Zealand Health and Disability Ethics Committee (Central Regional Ethics Committee). Further ethical approval was not required for this retrospective study.

Results

Fourteen hospices across a spread of rural and urban NZ submitted data from a total of 352 patients. There were 181 men and 171 women (with a median age of 72 years, range 21–96). Sixty-four patients died at home, 6 in a public hospital, 252 within a hospice IPU and 30 within a private hospital/nursing home setting.

Three hundred and two patients (86%) died of cancer-related disease and 51 (14%) died of non-malignant disease. The percentage of non-malignant deaths ranged from 0 to 35%. The most common cancers were gastrointestinal (24%), lung (17%), prostate and breast (both 7%), melanoma (6%), while non-malignant included chronic respiratory disease (4%) and heart failure (3%).

Ninety-five per cent of all patients received an opioid in their last 24 h. The patients who did not receive an opioid were not included in the analysis of opioid dosages.

Using data from a similar NZ benchmarking study carried out in 2005, the use of each opioid at the two time points is summarized in Table 1. The percentage refers to the number of patients who received at least one dose of that opioid.

Table 1 Usage of each opioid

<table>
<thead>
<tr>
<th>Percentage (%) of patients receiving specified opioid</th>
<th>2008</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>71</td>
<td>77</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Methadone</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>9.5</td>
<td>Nil</td>
</tr>
<tr>
<td>Other†</td>
<td>&lt;1</td>
<td>Nil</td>
</tr>
</tbody>
</table>

†One patient received tramadol drops and one patient received alfentanil.

The majority of patients in the current study received morphine alone (65%). Most patients received a single opioid; no patient was on more than two opioids (Table 2).

Dosage of opioids

In the last 24 h for patients receiving opioids (expressed as pMEDD), the geometric mean was 47.8 mg (median = 42.5 mg, range 1–1877.5 mg). Seventy-four per cent of patients received <100 mg/24 h, 92% of patients received <300 mg, 2.4% of patients >600 mg and only 1.5% of patients >1000 mg.

Independent-samples t-tests were conducted to compare the pMEDD scores (Table 3) according to gender, diagnosis (malignant vs non-malignant), whether on the LCP (yes or no) and place of death (hospice IPU vs private + public hospital + home). There was a significant difference in scores for diagnosis and LCP, but not for gender or place of death.

Inter-hospice variability

The range of means from the individual hospices was 30.5–80.7 mg. ANOVA testing showed that there was not a significant difference between the hospices’ means of pMEDD ($F_{13,333} = 1.264, P = 0.233$).

When this was repeated looking only at patients who died in an IPU, the between-hospice variation was reduced ($F_{13,228} = 0.879, P = 0.579$).

Table 2 Opioid combinations (n = 335)

<table>
<thead>
<tr>
<th>Opioid combinations</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine alone</td>
<td>209</td>
</tr>
<tr>
<td>Fentanyl alone</td>
<td>31</td>
</tr>
<tr>
<td>Oxycodone alone</td>
<td>28</td>
</tr>
<tr>
<td>Methadone alone</td>
<td>23</td>
</tr>
<tr>
<td>Morphine + methadone</td>
<td>14</td>
</tr>
<tr>
<td>Morphine + fentanyl</td>
<td>14</td>
</tr>
<tr>
<td>Other opioids/combos</td>
<td>16</td>
</tr>
</tbody>
</table>
Two-way ANOVA using diagnosis as the second independent variable to correct for its known influence on the pMEDD showed further reduction again of any divergence in the means ($F_{1,309} = 0.391, P = 0.959$) (Fig. 1).

The opioid footprint for each hospice is shown in Figure 2.

**Discussion**

The large majority (95%) of patients dying under hospice care in NZ received some form of opioid in their last 24 h of life. This is a relatively high percentage when compared with international data (82–89%)\(^1,17,18\) and similar to Australia (97%).\(^31\) The large National Hospice Outcomes Project\(^13\) in the USA noted that 89% of 1306 patients were on some opioid at the time of death.

Morphine remains the most commonly used opioid for hospice patients in NZ. Seventy-one per cent of patients received morphine compared with the 16.5% of patients who received the second most common opioid, fentanyl. Methadone has reduced from 23% of patients in the 2005 NZ benchmark study,\(^32\) to 10% in 2008 (Fig. 3). The difference has been taken up by increases in oxycodone and fentanyl use now that these opioids are subsidized by the government.

Usual practice is to use a single opioid. There is discussion in the literature about synergistic analgesia from combining two different opioids presumably by accessing different opioid receptor subtypes.\(^7,22,33\) Combination opioids are being used increasingly in some hospices, but this is not universal practice.

The opioid dose ranges described in this study are positively skewed. Most patients received relatively small

### Table 3 Comparison of pMEDD dose according to sex, type of life-limiting disease, LCP and place of death

<table>
<thead>
<tr>
<th>Geometric mean (mg) (95% confidence interval)</th>
<th>F statistic (degrees of freedom)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>47.8 (41.9–54.6)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>44.4 (37.0–53.3)</td>
<td>$F_{1,333} = 1.295$</td>
</tr>
<tr>
<td>Women</td>
<td>51.8 (42.6–63.0)</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>53.8 (46.6–62.1)</td>
<td>$F_{1,333} = 2.119$</td>
</tr>
<tr>
<td>Non-malignant</td>
<td>26.0 (19.1–35.3)</td>
<td></td>
</tr>
<tr>
<td>On LCP</td>
<td>63.1 (47.0–84.6)</td>
<td>$F_{1,333} = 4.479$</td>
</tr>
<tr>
<td>Not on LCP</td>
<td>44.4 (38.3–51.6)</td>
<td></td>
</tr>
<tr>
<td>Died in IPU</td>
<td>51.3 (43.7–60.1)</td>
<td>$F_{1,333} = 2.769$</td>
</tr>
<tr>
<td>Died elsewhere</td>
<td>39.9 (31.4–50.6)</td>
<td></td>
</tr>
</tbody>
</table>

**IPU**, inpatient unit; LCP, Liverpool Care Pathway; pMEDD, parenteral morphine equivalent daily dose.
doses, with 74% of patients using less than 100 mg parenteral morphine equivalent. There are concerns expressed in the literature regarding high-dose opioids. In this study we found that 2.4% of patients within usual practice required greater than 600 mg of pMEDD. A comparable study from the National Hospice Outcomes Project shows that 2.6% required opioid doses >600 mg intravenous morphine equivalent.

The geometric mean pMEDD of 47.8 mg opioid dose identified in this study appears comparable to previously published data (Table 4). However, there is no standard method for presenting the ‘average’ amount used. The log transformation method gives a normally distributed data group that can then be reliably used to generate the geometric mean for the dosage of drugs, and confidence limits allowing comparison between benchmarking sites. Analysis of single opioids will always be more meaningful than amalgamated analyses, especially when considering the variation in opioid conversion rates used in different centres. However, within an ongoing benchmarking study, consistency of conversion factors and analysis over time does allow for valid analyses of changes, although comparisons with other studies may be fraught.

There appears to be consistency in the dosages of opioids used across hospice teams within NZ, with no significant differences detected. The lesser requirement for opioids in non-malignant disease has been previously described. Although there is considerable overlap in symptomatology, cancer has the highest prevalence of severe pain. Analgesic needs have been rated against diagnosis in cancer, but we are not aware of similar studies in non-malignant disease.

Of interest was the finding that patients dying on the LCP received a higher opioid dosage than those not on the pathway. It is possible that those who are able to be diagnosed as dying in the hours or days before they die have different symptom burdens from those who die unexpectedly. It may be that those on the LCP had more attention given to their symptom control, or possibly

Table 4  Comparison of published figures for opioid use in the final 24 h of life

<table>
<thead>
<tr>
<th>Author</th>
<th>Country of origin</th>
<th>Patient numbers</th>
<th>Reported mean (mg)</th>
<th>Calculated mean pMEDD (mg)</th>
<th>Patient location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensor 2009</td>
<td>NZ</td>
<td>335</td>
<td>95</td>
<td>47.8</td>
<td>14 hospice teams</td>
</tr>
<tr>
<td>Brown 2008(^{35})</td>
<td>Scotland</td>
<td>40</td>
<td>OME 290</td>
<td>38</td>
<td>Hospice IPU</td>
</tr>
<tr>
<td>Wilcock and Chauhan 2007(^{13})</td>
<td>UK</td>
<td>72</td>
<td>OME 123.7</td>
<td>116(^{1})</td>
<td>Hospice IPU</td>
</tr>
<tr>
<td>Portenoy et al. 2006(^{13})</td>
<td>USA</td>
<td>725</td>
<td>IVME 371</td>
<td>124</td>
<td>13 hospice IPUs</td>
</tr>
<tr>
<td>Good et al. 2005(^{31})</td>
<td>Australia</td>
<td>229</td>
<td>OME 272/48 h</td>
<td>148</td>
<td>Tertiary IPU</td>
</tr>
<tr>
<td>Morita et al. 2001(^{15})</td>
<td>Japan</td>
<td>209</td>
<td>OME 54</td>
<td>54</td>
<td>Hospice IPU</td>
</tr>
<tr>
<td>Thorns and Sykes 2000(^{18})</td>
<td>UK</td>
<td>238</td>
<td>PME 55.5</td>
<td>Hospice IPU</td>
<td></td>
</tr>
<tr>
<td>Fainsinger et al. 2000(^{26})</td>
<td>Canada</td>
<td>100</td>
<td>pMEDD 73</td>
<td>3 hospice IPUs</td>
<td></td>
</tr>
<tr>
<td>Fainsinger et al. 2000(^{26})</td>
<td>Canada</td>
<td>100</td>
<td>145 mg pMEDD</td>
<td>Tertiary PCU</td>
<td></td>
</tr>
<tr>
<td>Bercovitch et al. 1999(^{14})</td>
<td>Israel</td>
<td>453</td>
<td>OME 230</td>
<td>Hospice IPU</td>
<td></td>
</tr>
</tbody>
</table>

\(^{1}\)Benchmarking only cancer patients admitted on regular opioids. IPU, inpatient unit; IVME, intravenous morphine equivalent; OME, oral morphine equivalent; PME, parenteral morphine equivalent; pMEDD, parenteral morphine equivalent daily dose.

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over treated. A recent study suggests that the institution of the LCP can lower symptom burden.\(^4^n\)

When considering deaths just in a hospice IPU, and correcting for the varying ratios of deaths due to malignant versus non-malignant deaths each hospice has, the mean dose of about 50 mg pMEDD is a reliable benchmark.

It is not the purpose of this benchmarking study to critique the practices of specific hospices. However, the opioid footprint gives hospice teams valuable information as to their own pattern of opioid prescribing. The Expert Working Group for the European Association of Palliative Care Network suggests that

clinician bias favours the selection of opioids with which the clinician has greatest familiarity and experience. Since the most familiar option may not be the best option, clinicians should be sensitive to this bias and should familiarize themselves with a range of therapeutic options, including facility with all of the opioid drugs available in their country.\(^9^n\)

Differences within NZ may reflect a range in prescriber familiarity and experience with those opioids available in NZ. It may reflect resource limitations, or that adequate pain control can best be attained with the expert use of a limited range of opioids. For those centres involved in specialist palliative physician training, and for trainees planning their training experience, it is appropriate to be cognisant of the variation in medication use between different centres.

**Conclusion**

This study describes current normal opioid prescribing practice for hospice-based practitioners in NZ. It appears to follow generally accepted guidelines for opioid prescribing. The great majority of patients have some opioid in the last 24 h of their lives, but the dosages used are conservative by international comparison. Given the variations in patient diagnoses, the amount of opioids prescribed by hospices is relatively uniform.

Comparisons using conversion ratios like the pMEDD are complex. Usefulness will depend on participating institutions using consistent ratios over time to track changes in prescribing practices. Differences in opioid use apparent between those on the LCP or not, and between malignant and non-malignant diagnoses, require further study.

These data allow participating hospices to reflect on their own practice, and provide a baseline for other countries, or networks, to aid in clinical governance and in continuing professional development.

**Acknowledgements**

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Benchmarking opioids
Intravenous zoledronic acid and oral alendronate in patients with a low trauma fracture: experience from an osteoporosis clinic


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Key words
osteoporosis, low trauma fracture, zoledronic acid, alendronate, bisphosphonate, treatment.

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Introduction

Osteoporosis-related low trauma fractures are associated with increased morbidity and mortality, and diminished quality of life. They also present a substantial public health burden, costing an estimated $AUD1.9 billion in direct health costs per annum in Australia. Patients who have sustained a low trauma fracture are at greater risk of further fractures. Oral bisphosphonate therapy has been shown to reduce the risk of subsequent fractures. Oral bisphosphonate therapy has been shown to reduce the risk of subsequent fractures. Despite strong evidence for the anti-fracture efficacy of oral bisphosphonates, their effectiveness is often compromised by a problematic dosing regimen, variable gastrointestinal absorption, and adverse events, leading to considerable non-adherence. Approximately 50% of patients prescribed oral bisphosphonate therapy have been reported to be non-adherent after 12 months.

A promising solution to the dosing problems of oral bisphosphonates is an annual intravenous infusion of the bisphosphonate, zoledronic acid (ZOL). Intravenous ZOL infusions given yearly have been reported to produce increases in bone mineral density (BMD) similar to those achieved with oral bisphosphonate dosing. Further, a recent randomized clinical trial has shown that a once-yearly infusion of ZOL in post-menopausal osteoporosis reduced the risk of vertebral fracture by 70% and hip fracture by 40% over a 3-year period, when compared with placebo. A further study of ZOL or placebo in patients who had sustained a hip fracture showed reduction of new clinical fracture and more importantly, improved survival with decreased mortality from any cause.

ZOL has recently become available in Australia as a Pharmaceutical Benefits Scheme-listed drug for post-menopausal women over the age of 70 years with a

Abstract

**Background/Aims:** Oral bisphosphonates have been shown to be effective in treating osteoporosis. However, there has been a significant problem with compliance. Newer intravenous bisphosphonates are available for osteoporosis management, but have not been compared with oral bisphosphonates in a clinical setting. The aim of this study was to compare the safety and effectiveness of intravenous zoledronic acid (ZOL) and oral alendronate (ALN) in osteoporotic patients following a low trauma fracture.

**Methods:** A non-randomized, retrospective cohort study was conducted of 169 patients with a low trauma fracture and reduced bone mineral density (BMD). Patients were treated with either an infusion of 4 mg ZOL or ALN 70 mg weekly. The outcomes measured were change in BMD after 12 months of treatment with either bisphosphonate, and new osteoporotic fractures. All adverse events were documented.

**Results:** Lumbar spine BMD (L2–L4) improved 5.6% in the ZOL group \(P < 0.001\) and 5.5% in the ALN group \(P < 0.001\). Total hip BMD improved 2% in the ZOL group \(P < 0.01\) and 2.5% in the ALN group \(P < 0.001\). There was no significant difference in BMD change between the groups. There were significantly more new fractures \(P < 0.001\) in the ZOL group (7.2%) than the ALN group (1%). The ZOL group were significantly older \(P < 0.01\) and had a significantly higher proportion of males \(P < 0.05\) at baseline. There were no serious adverse reactions in either group.

**Conclusion:** ZOL and ALN both produce a significant increase in BMD and are well tolerated in patients with osteoporotic, low trauma fractures. Yearly ZOL provides a safe, convenient alternative to weekly oral bisphosphonates.


Conflict of interest: None.
T-score of less than −3.0 or a history of low trauma fractures and in men with low trauma hip fractures. At Royal Prince Alfred Hospital (RPAH), we have been treating patients with low trauma fractures with either oral bisphosphonates or intravenous ZOL since 2003, the choice of drug based on clinical criteria.

There have been reports of the risk of osteonecrosis of the jaw (ONJ) with ZOL, which is rare in the yearly dosage used in osteoporosis.10 Despite its reported benefits and safety, there is still concern about ZOL, particularly among general practitioners and patients after adverse media reports.

To assess the safety and effectiveness of ZOL in clinical practice, we conducted a non-randomized, retrospective cohort study of patients presenting to our department with a low trauma fracture and reduced BMD. Patients were treated with either an annual 4 mg infusion of ZOL or 70 mg of oral alendronate (ALN) once weekly for at least 12 months. We measured the change in patient BMD after 1 year of therapy and assessed patients for new fractures and significant adverse events.

Patients and methods

We conducted a retrospective medical record audit of all patients entered in our First Fracture Program database between September 2003 and December 2006. The First Fracture Program initiative assesses all patients who have a low trauma fracture attending orthopaedic fracture clinics at RPAH, Sydney, Australia. The structure of the program has been reported previously.11

Study population

The study was approved by the Royal Prince Alfred Hospital Ethics Committee. A search of the First Fracture Program database identified 169 patients with a documented low-trauma fracture (radiological evidence and history of minimal trauma) who were treated with either ZOL or ALN for at least 12 months, and who had a BMD scan at the time of fracture and at least 12 months later (mean time to follow up was not significantly different between groups). Subjects were excluded if they had a prior history of oral bisphosphonate use longer than 3 weeks, prior history of intravenous bisphosphonate use, hypogonadism, hyperparathyroidism, prior glucocorticoid or hormonal therapy exposure, or had less than 90% reported compliance with oral medication regimens. Eleven subjects were excluded for one or more of the above reasons. All women included in the study were post-menopausal.

Fracture risk assessment

The 10-year probability of major osteoporotic fracture (hip, clinical spine, shoulder and forearm) was calculated for each patient using the World Health Organizations’ Fracture Risk Assessment Tool (FRAX). The application of this assessment tool has been extensively described and validated elsewhere.12,13 The clinical risk factors used in the algorithm were age, sex, body mass index, hip BMD T-score, prior fragility fracture (yes/no), parental history of hip fracture (yes/no), long-term use of oral glucocorticoids (yes/no), rheumatoid arthritis (yes/no), other causes of secondary osteoporosis (yes/no), daily alcohol consumption of >3 standard units daily (yes/no). The UK algorithm was chosen as it most closely reflects the epidemiology of our study population.

BMD and laboratory measurements

Baseline and follow-up BMD was carried out at lumbar spine (L2-4) and total hip using dual-energy X-ray absorptiometry (Lunar Prodigy, General Electric Co., Madison, WI, USA) in the Department of Rheumatology at RPAH. All BMD measurements were carried out by the osteoporosis nurse on the same machine. Serum 25-hydroxy vitamin D₃, parathyroid hormone, and testosterone in men, were also measured at baseline.

Bisphosphonate therapy

Patients were reviewed by a staff rheumatologist shortly after their initial fracture and osteoporosis nurse interview. Those deemed to require bisphosphonate therapy were prescribed either 70 mg alendronate (Fosamax, Merck Sharp and Dohme, South Granville, NSW, Australia) once weekly, or a once-yearly 4 mg i.v. infusion of ZOL (Zometa, Novartis Pharmaceuticals, North Ryde, NSW, Australia). The decision on whether to prescribe oral or i.v. bisphosphonate was determined by the physician in consultation with the patient, and took account of factors such as likely compliance, comorbidities, contraindications and patient preference. Some patients were also prescribed vitamin D and/or calcium supplements, depending on their baseline 25-hydroxy vitamin D₃ level and reported calcium intake.

Follow up

Patients were contacted 1 month after therapy was initiated to assess for adverse events, dosing difficulties and compliance. Patients were reassessed at approximately 12 months by the ON, who carried out a follow-up BMD
measurement and undertook another interview to confirm compliance and assess for adverse events and new major osteoporotic fractures (hip, clinical spine, shoulder and forearm). Patients were excluded if self-reported compliance with oral medication was less than 90%.

Outcomes and statistics
The primary outcomes assessed were the percentage change in absolute BMD at both lumbar spine and total hip, and the occurrence of new major osteoporotic fractures (hip, clinical spine, shoulder and forearm). Significant adverse events were also recorded. Within-group changes from baseline were measured using Student’s t-tests. As the sample sizes differed between the groups and some of the variables measured were skewed, non-parametric analyses were used to compare the two groups. Mann–Whitney U-tests were used to compare baseline variables and BMD change, and χ² tests were used to compare the number of new fractures. For BMD measurements, the possible effects of baseline vitamin D level and fracture risk were adjusted for using analysis of covariance. Results were considered significant at $P<0.05$. Statistical analyses were carried out using SPSS 13.0 (SPSS, Chicago, IL, USA). All data entry was checked by an administrative clerk.

Results
Baseline characteristics
There were 70 patients in the ZOL group and 99 patients in the ALN group (Table 1). At baseline, the ZOL group were significantly older ($P<0.01$) and had significantly higher proportion of males ($P<0.05$). The average 10-year probability of major osteoporotic fracture according to the FRAX algorithm (without treatment) was 18.2% in the ZOL group, and 14.8% in the ALN group (no significant difference $P = 0.84$). There was also no significant difference between the two cohorts at baseline with respect to vitamin D levels or BMD T-score at either lumbar spine or total hip.

Bone mineral density
There was a significant improvement in absolute BMD for both groups at the lumbar spine and total hip (Fig. 1). When compared with baseline, absolute lumbar spine BMD improved by 5.65% in the ZOL group ($P<0.001$) and by 5.9% in the ALN group ($P<0.001$). At the total hip, absolute BMD improved by 2% in the ZOL group ($P<0.01$) and by 2.5% in the ALN group ($P<0.01$) when compared with baseline. The percentage change in BMD was not statistically different between the two groups at either lumbar spine ($P = 0.624$) or total hip ($P = 0.968$). The results did not change after adjusting for baseline vitamin D level and fracture risk.

Subsequent fractures and adverse events
There was a statistically significant increase in the number of major osteoporotic fractures in the ZOL group

Table 1 Baseline demographics and bone mineral density T-scores at lumbar spine and total hip

<table>
<thead>
<tr>
<th></th>
<th>ZOL group (n = 70)</th>
<th>ALN group (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male : female ratio</td>
<td>22:48 (1:2.2)*</td>
<td>20:79 (1:3.9)</td>
</tr>
<tr>
<td>Age at start of treatment (years)</td>
<td>71 ± 12**</td>
<td>65 ± 11</td>
</tr>
<tr>
<td>10-year probability of major osteoporotic fracture (FRAX)</td>
<td>18.2 ± 11.1</td>
<td>14.8 ± 7.0</td>
</tr>
<tr>
<td>Vitamin D level (nmol/L)</td>
<td>52.4 ± 22.7</td>
<td>60.3 ± 26.5</td>
</tr>
<tr>
<td>Baseline BMD T-score (lumbar spine)</td>
<td>−2.2 ± 1.48</td>
<td>−2.17 ± 1.08</td>
</tr>
<tr>
<td>Baseline BMD T-score (total hip)</td>
<td>−2.08 ± 0.96</td>
<td>−1.79 ± 0.93</td>
</tr>
</tbody>
</table>

* $P < 0.05$, ** $P < 0.01$, when compared with ALN group. Values are mean ± standard deviations. ALN, alendronate; BMD, bone mineral density; ZOL, zoledronic acid.
when compared with the ALN group (P < 0.001) (Table 2). There were five (7.2%) new major osteoporotic fractures (two hip, two shoulder and one forearm) within 1 year of starting treatment in the ZOL group. One major osteoporotic fracture (hip) was recorded in the ALN group (1%).

There were no serious adverse events, including ONJ or atrial fibrillation, reported in either group. Nine minor adverse events were reported in the ZOL group: three (4.3%) episodes of flu-like reaction (fever, myalgia and bone pain), three (4.3%) episodes of mild bone ache, one (1.4%) episode of chest pain for 3–4 min during infusion, and one (1.4%) episode of nausea and vomiting post infusion. There were also three minor adverse events reported in the ALN group: one episode (1%) of nausea and vomiting, and two episodes (2%) of gastro-oesophageal reflux following ingestion of ALN.

**Discussion**

Intravenous ZOL has been advanced as a potential solution to the dosing and compliance problems of oral bisphosphonates. Adherence to oral bisphosphonates is problematic; the drug must be taken with a full glass of water on an empty stomach, and the patient must remain upright for 30 min after ingesting the medication. Oral bisphosphonates can also produce side-effects, including upper gastro-intestinal irritation, particularly if the dosing regimen is not followed.

Compliance with oral bisphosphonates has been reported as low as 50%, with most patients reported to be taking less than 80% of their prescribed pills at 12 months. In contrast, once-yearly intravenous ZOL therapy guarantees all patients receive the intended dose of bisphosphate, and negates the dosing and adherence problems associated with oral bisphosphonates.

This study was carried out to compare ‘real life’ use of ZOL with ALN therapy. It is interesting to note that despite similar improvements in BMD at both hip and lumbar spine, there were significantly more new major osteoporotic fractures (P < 0.001) in the ZOL group (7.2%) compared with the ALN group (1%). When the FRAX tool was applied to both groups, there appeared to be no significant difference in the 10-year probability of major osteoporotic fracture between the groups. This study was not randomized and the differences seen may represent the use of ZOL in older patients and more males, especially considering the pathogenesis of osteoporosis may be different between men and women. The differences may also have been due to unrecognized biases in baseline characterisation, such as a frailer group with a higher falls risk, which was not formally assessed. It will take randomized, comparative studies of ALN with ZOL to clarify this issue.

The decision to exclude non-compliant patients was made to help determine whether differences in BMD change or fracture rate were due to drug effect rather than patient compliance. By excluding patients who were non-compliant with ALN, the fracture numbers were potentially biased against ZOL, especially given that one of the main advantages of ZOL in clinical practice is that compliance with the drug is 100%. Ideally, future analyses should be conducted on an intention-to-treat basis including all patients who were prescribed alendronate. Further, the present study contained a relatively small number of patients for a fracture end-point study, with only one fracture in the ALN group and five in the ZOL group. While this was found to be statistically different, future studies also require larger study populations to increase the power and reliability of such statistical calculations.

Although ONJ has been a well publicized complication of intravenous ZOL use, there were no cases of ONJ reported in any of the patients in our study. This finding is consistent with a recent placebo-controlled trial of ZOL use for osteoporosis in 3889 postmenopausal women which also reported no spontaneous cases of ONJ, though it did find a significantly higher incidence of serious atrial fibrillation in those receiving ZOL. One patient from the ZOL group in our study experienced a period of chest pain during the infusion, although there

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Age</th>
<th>Gender</th>
<th>Fracture site</th>
<th>Baseline BMD hip</th>
<th>Baseline BMD lumbar</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZOL</td>
<td>71</td>
<td>Male</td>
<td>Bilateral rib</td>
<td>−3.3</td>
<td>−2.2</td>
</tr>
<tr>
<td>ZOL</td>
<td>91</td>
<td>Female</td>
<td>Shaft of femur</td>
<td>−2.5</td>
<td>−1.8</td>
</tr>
<tr>
<td>ZOL</td>
<td>62</td>
<td>Female</td>
<td>Distal fibula</td>
<td>−1</td>
<td>−2.9</td>
</tr>
<tr>
<td>ZOL</td>
<td>62</td>
<td>Male</td>
<td>Sacrum</td>
<td>−2.6</td>
<td>−4.1</td>
</tr>
<tr>
<td>ZOL</td>
<td>64</td>
<td>Female</td>
<td>Proximal humerus</td>
<td>−0.7</td>
<td>−2.5</td>
</tr>
<tr>
<td>ALN</td>
<td>81</td>
<td>Female</td>
<td>Neck of femur</td>
<td>−2</td>
<td>−1.4</td>
</tr>
</tbody>
</table>

ALN, alendronate; BMD, bone mineral density; ZOL, zoledronic acid.
was no electrocardiogram evidence to suggest that this was due to atrial fibrillation. The most common side-effect reported in the ZOL group was a brief flu-like reaction shortly after infusion (4.3%) or mild bone pain (4.3%). These side-effects were manageable with regular paracetamol.

**Conclusion**

Intravenous ZOL overcomes the dosing and compliance issues commonly seen with oral bisphosphonates, and provides a safe alternative. In clinical use in a large teaching hospital, ZOL has been shown to be safe and effective.

**References**

JAK2 mutations in Asian patients with essential thrombocythaemia

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Key words
JAK2 mutations, essential thrombocythaemia, cytoreductive therapy, bleeding, thrombosis.

Abstract
Background/Aim: JAK2V617F is an acquired mutation present in a considerable proportion of patients with chronic myeloproliferative disorders. Its reported prevalence in European and US studies of patients with essential thrombocythaemia (ET) is 23–57%. This study was conducted to determine the prevalence of the JAK2 mutation in Asian ET patients, and to examine their disease profile.

Methods: Asian patients with ET were either recruited to the study or registry data were analysed retrospectively. Blood samples were collected for analysis of JAK2 mutation status during routine patient follow up. Clinical data on these patients (including demographics and disease profiles) and complications at diagnosis were recorded.

Results: The JAK2 mutation was detected in 35/102 (34%) patients. Females were more likely than males to have JAK2 mutation (P = 0.031). At diagnosis, JAK2-mutated patients were found to be older (P = 0.012), have higher leucocyte counts (P = 0.036) and high-risk disease (P = 0.039). There were no other statistically significant differences between mutated and wild-type JAK2 ET patients.

Conclusion: The prevalence of JAK2 mutations in this population of Asian ET patients was 34%. Patients with the JAK2 mutation were significantly more likely to have high-risk disease. Further studies are required to assess the role of JAK2 mutations in risk stratification in ET and compare the phenotype of Asian patients with other populations.

Introduction
The chronic myeloproliferative disorders include a number of clonal haematological malignant diseases, the most common being essential thrombocythaemia (ET), polycythaemia vera (PV) and idiopathic myelofibrosis (IMF).1 Until recently, very little was known about the genetic basis of these conditions. In 2005, however, several publications reported identification of a genetic marker,2–4 which described a dominant gain-of-function somatic JAK2V617F mutation in exon 14 1849G>T present in the chronic myeloproliferative disorders.

This acquired JAK2V617F mutation leads to substitution of phenylalanine for valine at amino acid position 617 (V617F) of the JAK2 protein. It has been detected in the majority of patients with PV2–6 and less frequently in patients with ET (23–57%)2–5 and IMF (35–57%)2–5,10 and reportedly results in expression of a constitutively activated tyrosine kinase that confers proliferative and survival advantages on haematopoietic precursors.3,4 The molecular basis for ET in patients without the JAK2V617F mutation remains unclear, although abnormalities in the c-mpl receptor have been implicated in some patients.1,11

The clinical consequences of the JAK2 mutation in patients with ET have been analysed in retrospective studies, mainly in European and US populations.6,8,9,12–14 Some differences between ET patients with wild-type and mutated JAK2 have been suggested.6,8,9,12–14 For example, one study reported that patients with JAK2 mutations and ET, PV and IMF were older at diagnosis, with higher haematocrit and haemoglobin levels and lower erythropoietin levels.12 Furthermore, these patients had a higher probability of the presence of leucocytosis, splenomegaly and thrombotic events than their wild-type JAK2 counterparts.12 Some other studies also found JAK2-mutated ET to be associated with higher haemoglobin levels9,13 and an increased risk of thrombosis.13,14 However, an increased thrombotic risk was not seen by Wolanskyj et al. while Campbell et al. found that wild-type JAK2 patients had clinical and laboratory characteristics of a myeloproliferative disorder and those with JAK2 mutations had features resembling PV.8,9 Wolanskyj et al...
concluded that although the presence of JAK2 mutation in ET appears to confer a PV phenotype, this might not be relevant to treatment.9

Only a few small studies have assessed the prevalence and phenotypic characteristics of JAK2 mutations among Asian ET patients. These suggest that the prevalence of JAK2 mutation among Chinese, Korean and Taiwanese patients is 46–59%.15–17

The aim of this study was to determine the prevalence of the mutated JAK2 gene in Asian patients with ET and investigate whether JAK2 mutation has an impact on the disease profile. We considered whether the disease profile of ET patients with the JAK2 mutation is different from patients without the mutation (wild-type JAK2) and thus whether it should influence our management of these patients.

Materials and methods

Patient recruitment

Patients were recruited from the myeloproliferative disease registry (consisting of more than 250 patients with ET, mostly of Asian origin) of the Haematology Department at the Singapore General Hospital). Patients were either recruited to the study between April 2006 and December 2007 (n = 95) or analysed retrospectively from registry data (n = 7). Inclusion criteria were a diagnosis of ET, Asian ancestry and the ability to give informed consent. Before 2001, a diagnosis of ET was based on the Polycythaemia Vera Study Group (PVSG) criteria (1997)18 and from 2001 onwards, on the World Health Organization (WHO) criteria (2001).19 Patients were excluded if they had other myeloproliferative diseases or haematological disorders, or did not fulfil the inclusion criteria. Bone marrows were reviewed for the patients diagnosed using PVSG criteria to exclude those with early myelofibrosis. Blood samples were collected for analysis of JAK2 mutation status during routine patient follow up. Clinical data on these patients, including demographics and disease profiles, were gathered retrospectively from the myeloproliferative disease registry, a computerized database, which was set up with Ethics Committee approval. Complications at diagnosis were recorded: these were defined as complications occurring at presentation or within the month before ET diagnosis.

Patients were assigned a risk category at diagnosis. High-risk status was assigned if patients were 60 years or older, had a history of thrombosis, or a platelet count >1500 × 10^9/L. Patients who did not meet these criteria and had no cardiovascular risk factors were classified as low risk. Intermediate-risk classification was designated to those who did not meet the criteria for low- or high-risk groups.20 Patients were subject to regular follow up as part of their normal management. The interval of their routine follow up varied between 1 and 4 months as determined by their platelet counts.

Determining JAK2V617F status

Sample collection and processing

Peripheral blood samples (3–5 mL) were drawn into ethylene diamine tetraacetic acid-anticoagulated tubes and mononuclear cells were prepared with the use of Ficoll gradient centrifugation. Granulocytes were isolated and collected, and genomic DNA was extracted using the PureGene® DNA isolation kit protocol (Gentra Systems, Minneapolis, MN, USA) according to the manufacturer’s instructions.

Mutation screening

DNA samples were evaluated for the presence of the guanine to thymine substitution in JAK2 exon 14 (which results in a valine to phenylalanine substitution at codon 617 (V617F)) using BsaX1 restriction enzyme digestion methods.21 For direct sequencing, the polymerase chain reaction (PCR) products were purified and sequenced directly using the ABI 310 Prism® Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) and appropriate primers.

Data analysis

Patients were classified as having either mutated or wild-type JAK2. Data from the myeloproliferative disease registry were then gathered retrospectively for each patient, and compared across the two groups. Parameters investigated included: age at diagnosis; haemoglobin/haematocrit levels; disease complications; and type of cytoreductive therapy prescribed.

Statistical methods

Data from patients heterozygous and homozygous for the JAK2 mutation were pooled as mutated JAK2 patients for the purpose of analysis. Differences between mutated and wild-type JAK2 patients were analysed using Student’s t-test for continuous data and Mann–Whitney U-test for categorical data. SPSS Version 13 (SPSS, Chicago, IL, USA) software was used to carry out the analyses, with P < 0.05 being considered statistically significant.
Results

Patient characteristics and disease profile at diagnosis

Table 1 shows the demographic, clinical and laboratory characteristics of the 102 ET patients included in the myeloproliferative disease registry who provided informed consent to be tested for the JAK2 mutation. In total, 52 female and 50 male patients were enrolled in the study; the majority of patients were of Chinese ethnicity (79%). The overall prevalence of the JAK2 mutation was 34% (35/102); 34 patients (33%) were heterozygous mutant, and one patient (1%) was homozygous mutant. The JAK2 mutation was significantly more common in females than males ($P = 0.031$).

In terms of their disease profile, JAK2-mutated patients were significantly older at diagnosis ($P = 0.012$), had higher presenting leucocyte counts ($P = 0.036$) and higher thrombotic risk ($P = 0.039$) at diagnosis. JAK2-mutated patients also had higher bone marrow cellularity ($P = 0.01$). No other differences between mutated and wild-type JAK2 were recorded.

Symptoms at diagnosis were reported by 27% and 29% of wild-type JAK2 and JAK2-mutated patients, respectively. The most common symptoms were headache (13/102, 13%) and paraesthesia or numbness (8/102, 8%). Four patients were pregnant at diagnosis, all of whom had wild-type JAK2 and were asymptomatic. Their platelet counts ranged from $995 \times 10^9/L$ to $1966 \times 10^9/L$.

Bone marrow cytogenetics were evaluated in 85 patients. Of these, 80 (94%) cases were normal. The

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of patients with essential thrombocythaemia ($n = 102$) at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wild-type phenotype ($n = 67; 65.7%$)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>54 (80.6%)</td>
</tr>
<tr>
<td>Malay</td>
<td>10 (14.9%)</td>
</tr>
<tr>
<td>Indian</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Other Asian</td>
<td>2 (3.0%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female ($n = 52, 51.0%$)</td>
<td>29 (55.8%)</td>
</tr>
<tr>
<td>Male ($n = 50, 49.0%$)</td>
<td>38 (76.0%)</td>
</tr>
<tr>
<td>Mean age at diagnosis (years)</td>
<td>46.19 (25–85)</td>
</tr>
<tr>
<td>JAK2 genotype</td>
<td></td>
</tr>
<tr>
<td>Heterozygous mutant</td>
<td>NA</td>
</tr>
<tr>
<td>Homozygous mutant</td>
<td></td>
</tr>
<tr>
<td>Risk category</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>26 (38.8%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>17 (25.4%)</td>
</tr>
<tr>
<td>High</td>
<td>24 (35.8%)</td>
</tr>
<tr>
<td>Initial platelet count ($\times 10^9/L$)</td>
<td>964.9 (413–2310)</td>
</tr>
<tr>
<td>Leucocyte count ($\times 10^9/L$)</td>
<td>10.3 (4.6–18.6)</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>13.5 (8.0–18.7)</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>40.6 (23.7–54.4)</td>
</tr>
<tr>
<td>Bone marrow cellularity (72 cases)</td>
<td></td>
</tr>
<tr>
<td>Hypocellular</td>
<td>2 (3.9%)</td>
</tr>
<tr>
<td>Normocellular</td>
<td>30 (58.8%)</td>
</tr>
<tr>
<td>Hypercellular</td>
<td>19 (37.3%)</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>4 years 357.1 days (0.05 years–14 years 40.0 days)</td>
</tr>
<tr>
<td>Symptoms at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18 (26.9%)</td>
</tr>
<tr>
<td>No</td>
<td>49 (73.1%)</td>
</tr>
<tr>
<td>Cytoreductive therapy</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>19 (28.4%)</td>
</tr>
<tr>
<td>Yes</td>
<td>48 (71.6%)</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14 (20.9%)</td>
</tr>
<tr>
<td>Yes</td>
<td>53 (79.1%)</td>
</tr>
</tbody>
</table>

Bold represents $P$ values showing significance.
remaining five patients showed, respectively, a pericentric inversion of chromosome 9, trisomy 8, trisomy 9, del 3 and a complex rearrangement of chromosomes 3 and 20. Cytogenetic data were not available in the remaining 17 patients because inadequate bone marrow samples were taken or the treating clinician did not order the test. There was no statistically significant difference between the cytogenetics of JAK2-mutated and wild-type JAK2 patients.

At diagnosis: five (5%) patients had disease complications (four suffered cerebrovascular accidents (CVA) (two wild-type JAK2, two heterozygous mutant JAK2), and one presented with fits (wild-type JAK2)). Before diagnosis, in total, nine patients (9%) suffered arterial thrombosis; three patients (3%) had experienced an acute myocardial infarction (AMI) (two wild-type, one heterozygous mutant JAK2); four patients (4%) suffered CVA (one wild-type JAK2, three heterozygous mutant JAK2); and two patients (2%) (both wild-type JAK2) had transient ischaemic attacks (TIA). The only patient with a venous thrombosis (heterozygous mutant JAK2) was diagnosed with a portal vein thrombosis before ET was diagnosed. All of these patients belonged to the high-risk category. Owing to the low numbers, no statistical analysis was carried out on these findings.

Events during follow up

Arterial thrombotic events occurred in two high-risk patients (one AMI and one TIA, both treated with aspirin, anagrelide and hydroxyurea) and one low-risk patient (CVA, treated with aspirin, ticlopidine, anagrelide and hydroxyurea). Venous thrombosis was not reported in any patient during the follow-up period. Minor bleeding complications were reported by 16 patients, 12 of whom were taking an antiplatelet agent. One patient, who was not on any antiplatelet agent, had a massive haemoptysis requiring bronchial embolization. There was no evidence for a higher incidence of thrombotic events or bleeding complications among JAK2-mutated patients.

Among ET patients with the wild-type JAK2 gene, one transformed to myelogenous leukaemia and another transformed to myelofibrosis. Three deaths were recorded during follow up: two patients died of sepsis (both wild-type JAK2) and one of ischaemic heart disease caused by thrombosis (heterozygous mutant JAK2; patient treated with aspirin and hydroxyurea).

Treatment

A total of 74/102 (73%) patients received cytoreductive therapy: the majority received anagrelide (n = 49) or hydroxyurea (n = 71) or a combination of these agents (n = 23). Interferon was prescribed to six patients (five were pregnant and one was 16 years of age and prescribed interferon to avoid the potential leukaemogenicity of hydroxyurea). An antiplatelet agent (mainly aspirin) was prescribed for 81/102 (79%) patients. A combination of a cytoreductive agent and an antiplatelet agent was prescribed in 61/102 (60%) patients.

A total of 4/102 (4%) patients required plateletapheresis. Two patients, with platelet counts of 1543 × 10^9/L and 2742 × 10^9/L respectively, developed hyperviscosity symptoms, needing urgent plateletapheresis. The third patient was in her first pregnancy with a platelet count of 1393 × 10^9/L. All of these patients had wild-type JAK2. The final patient, with a heterozygous mutant JAK2, had a platelet count of 4450 × 10^9/L when plateletapheresis was initiated.

Discussion

The prevalence of the JAK2 mutation in our sample of ET patients of mixed Asian descent was 34%. Several predominantly European and US studies reported frequencies of the mutated JAK2 gene in ET patients ranging from 23% to 57%\(^2\)\(^\text{-}\)\(^5\),\(^7\)\(^\text{-}\)\(^9\),\(^17\) while Speletas et al.\(^1\) reported an even higher prevalence of 69%. There are several possible reasons for the diversity in prevalence rates, including the varying sensitivity of different techniques used to detect the mutation. In particular, allele-specific PCR assays may detect the mutation at a higher frequency than direct sequencing. The adoption of different diagnostic criteria may also have influenced the results. In the WHO classification, patients with low fibrin localization in bone marrow are classified as having IMF rather than true ET.\(^1\) Hence, some of the studies using the PVSG criteria to diagnose ET may include a proportion of ET patients who actually have IMF or PV according to the WHO criteria.\(^1\) In our cohort, 19% of patients were diagnosed using the PVSG criteria and the remaining 81% using the WHO criteria. As the majority of the patients in this study were diagnosed using the WHO criteria, we felt that the inclusion of IMF or PV patients should have minimal impact on our results. Hence, our results should be representative of true ET patients.

While large-scale studies on the prevalence of the JAK2 mutation in Asian cohorts of patients with ET are lacking, recent studies have reported prevalence rates ranging from 46% to 59%.\(^1\)\(^5\)\(^\text{-}\)\(^1\) In a Korean study, JAK2 mutations were detected in 46% of 26 ET patients.\(^1\) Diagnosis of ET was based on the WHO criteria since 2001 and PVSG criteria before 2001. The JAK2V617F mutation was detected in 40/68 (59%) Chinese patients with ET,\(^1\) while in a study of 88 Taiwanese patients with myeloproliferative disorders and other haematological
diseases, the JAK2 mutation was present in 59% (29/49) of patients with ET. While these rates are higher than reported in the present study, the sample sizes in these studies were small (ranging from 26 to 68 patients) and as such they may not be representative of wider Asian populations. A further explanation for the difference in prevalence may be the use of allele-specific PCR in two of these studies, as outlined previously. When comparing prevalence rates across Asian studies it is also important to consider whether the ethnic mix of patients differs between studies (the aforementioned studies included Chinese, Malay and Indian patients, as well as those of other Asian ancestry).

In the present study, JAK2-mutated patients were more likely to be female, older at diagnosis, had higher presenting leucocyte counts, higher risk disease at diagnosis and higher bone marrow cellularity. Similarly, Speletas et al. reported that patients in Greece with the JAK2 mutation were older ($P = 0.02$) and had a higher probability of leucocytosis (threefold) and splenomegaly (twofold). In contrast with our study, however, they found that patients with the JAK2 mutation experienced a higher incidence of thrombosis (twofold) compared with wild-type JAK2 patients. Finazzi et al. also reported higher white cell counts and bone marrow cellularity in patients with the JAK2 mutation, and a risk of thrombosis twice that of their JAK2 wild-type counterparts, while a study of 95 Chinese ET patients found a thrombosis twice that of their JAK2 wild-type counterparts. Finazzi et al., reported that patients in Greece with the JAK2 mutation were older ($P = 0.02$) and had a higher probability of leucocytosis (threefold) and splenomegaly (twofold). In contrast with our study, however, they found that patients with the JAK2 mutation experienced a higher incidence of thrombosis (twofold) compared with wild-type JAK2 patients. Finazzi et al. also reported higher white cell counts and bone marrow cellularity in patients with the JAK2 mutation, and a risk of thrombosis twice that of their JAK2 wild-type counterparts, while a study of 95 Chinese ET patients found a thrombosis twice that of their JAK2 wild-type counterparts. Finazzi et al. found that patients in Greece with the JAK2 mutation were older ($P = 0.02$) and had a higher probability of leucocytosis (threefold) and splenomegaly (twofold). Hence, hydroxyurea, a myelosuppressive agent, may be more effective in decreasing thrombotic events than anagrelide in patients with raised white cell counts. An elevated haemoglobin/haematocrit may also contribute to risk of thrombosis. Hence, hydroxyurea may be of benefit to such patients as it decreases the haemoglobin/haematocrit. However, anagrelide may be the preferred agent of choice in younger patients as some physicians are concerned about the long-term leukaemogenic effect of hydroxyurea.

**Conclusions**

The prevalence of JAK2 mutation in our Asian ET patients was 34%. These patients were significantly more likely to be classified as having high-risk disease; however, further prospective studies are required to assess the role of the JAK2 mutation in risk stratification in ET and whether there are differences in the phenotype of Asian patients compared with European populations.

**Acknowledgements**

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Wong et al.

mutation in essential thrombocythemia. 
Brief Communications

Antitopoisomerase antibody positivity predates nailfold capillaroscopy abnormalities in scleroderma. Postulated classification of ‘prescleroderma’

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Key words
autoantibody, nailfold capillaroscopy, prediagnostic staging, scleroderma.

Abstract

In a patient with early topoisomerase antibody-positive scleroderma, antinuclear antibody positivity was fortuitously observed to predate nailfold capillaroscopy changes. Using this case as a template, the prediagnostic phase of the presumed multifactorial disease may be divided into 5 temporal phases – phase 1 representing conception and intrauterine environment, phase 2 representing the extraterine environment predating environmental exposure; phase 3 representing the early post-environmental exposure interval with no detectable perturbed body status; phase 4 representing the post-environmental exposure interval characterized by autoantibody production and microvascular changes, and phase 5, the symptomatic clinical prediagnostic interval (Raynaud’s, skin, musculoskeletal, gastrointestinal, cardiorespiratory) prompting scleroderma diagnosis. Temporal classification of prescleroderma aids in both the understanding and definition of scleroderma ‘onset’. If altered nailfold capillaries and autoantibodies develop at comparable rates, and if the findings from this case – that autoantibody changes precede microvascular changes – are truly representative of the preclinical disease phase, then these findings argue that the evolution of the disease is from within the vessel outwards, rather than vice versa.

Scleroderma is a connective tissue disease of poorly defined, probably multifactorial aetiology with peak onset around the fifth to sixth decades. Its clinical onset is often heralded by the development of Raynaud’s phenomenon which, in the limited cutaneous disease subtype may predate the second disease symptom by two decades. At the time of clinical presentation, antinuclear antibody is usually present in high titre and nailfold capillaroscopy is classically abnormal. Indeed, the presence of high titre antinuclear antibody and abnormal nailfold capillaroscopy, both of which are independent antecedents for scleroderma, is often used to delineate primary Raynaud’s from Raynaud’s secondary to an evolving connective tissue disorder, including scleroderma. However, the prediagnostic temporal evolution of scleroderma – including the temporal relationship between antinuclear antibody positivity and abnormal nailfold capillaroscopy – remains incompletely determined. The preclinical staging of the disease is also undefined.

We report a patient in whom the temporal relationship between antinuclear antibody positivity and nailfold capillaroscopy changes was fortuitously observed. The patient has evolving antitopoisomerase antibody-positive disease. We theorize about the temporal evolution of the prediagnostic phases of scleroderma using this case as a template, and propose a temporal staging for these prediagnostic phases. This proposed temporal classification may be useful in defining scleroderma disease onset, currently a clinical definition.

A 25-year-old woman first presented to her medical practitioner in May 2005 with a 12-month history of increased fatigue and weight loss, and a 1-month history of stiff, swollen painful fingers and feet. Antitopoisomerase antibody was detected following which she was referred for a rheumatological opinion. Nailfold capillaroscopy was normal. During the ensuing months she developed biphasic Raynaud’s, purplish discolouration over the metacarpophalangeal joints, symptomatic synovitis, joint early morning stiffness and reduced ability to make a fist. Scleroderma was diagnosed in December 2005. Repeat nailfold capillaroscopy showed dilatation of capillaries with an obvious degree of capillary irregularity with increased intravascular red cell aggregation.

Clinical examination revealed sclerodactyly, slowly pitting skin oedema over the fingers, periungual erythema and mild neck flexor weakness. The rest of the
musculoskeletal, cardiac and respiratory examination was normal.
Investigations demonstrated normal full blood count, erythrocyte sedimentation rate and C-reactive protein, serum creatinine, creatine kinase, liver function studies, gamma globulins, rheumatoid factor, muscle magnetic resonance imaging and electrocardiogram. Antinuclear antibody was positive in a titre of 1:320 (nucleolar pattern). High resolution computed tomography demonstrated a mild lower zone centrilobular thickening, but without features to suggest alveolitis or bibasilar fibrosis. Lung function studies showed a borderline reduced diffusion capacity.

Discussion
This case is reported for two reasons. First, it allows postulation of a number of discrete, possibly overlapping phases of scleroderma prediagnosis. Second, it demonstrates the previously unclarified temporal relationship between abnormal autoantibody status and nailfold capillaroscopy abnormalities in scleroderma.

Using silica-induced disease as an environmental model, we tentatively propose the following temporal, sometimes overlapping, phases (Fig. 1). The first – Phase 1 – represents the genetic load and intrauterine environment.1-4 Phase 2, of variable duration, represents the extraterine phase predating environmental exposure. In silica-induced scleroderma, this phase often lasts into early to mid-adulthood because this is classically when intense silica exposure often first occurs in an occupational capacity.5 Phase 3 represents the interval immediately postdating the initial environmental insult, before which there is any detectable in vivo response to the environmental stimulus. This interval is currently of undefined duration, being dependent on both the investigative instrument used and its sensitivity. Phase 4 represents the postexposure interval characterized by asymptomatic perturbations of body status including autoantibody production and microvascular changes. Phase 5 represents the symptomatic prediagnostic interval often characterized by Raynaud’s, skin, musculoskeletal, gastrointestinal and/or cardiorespiratory symptoms which prompt scleroderma diagnosis. Phase 6 represents scleroderma diagnosis. Phase 7 represents the postdiagnostic early, mid- and late postdiagnostic clinical complications.

If this case’s findings are truly representative, that is, that perturbed autoantibody positivity precedes abnormal nailfold capillaries, then an argument may be made into further segregating Phase 4 into two: (i) autoantibody positive and normal nailfold capillaroscopy, and (ii) autoantibody positive and abnormal nailfold capillaroscopy phases. However, whether or not Phase 4 may be split cannot realistically be made from this case alone, and will need confirmation from similar independent studies.

The disparity between autoantibody profile and nailfold capillaroscopy abnormalities was possible because Phases

![Figure 1](https://example.com/figure1.png)

**Figure 1** Postulated temporal staging of scleroderma. ANA, antinuclear antibody.
4 and 5 overlapped in this patient, that is, the symptomatic Phase 5 prompted autoantibody and nailfold capillaroscopy observations by an experienced capillaroscopist (MM) both at the patient's initial presentation and again 7 months later. This case adds to our understanding of Phase 4, where it was noted that the patient's altered autoantibody status, specifically antitopoisomerase positivity, predated nailfold capillaroscopy changes. This observation has not previously been reported, to the best of our knowledge in scleroderma patients, although low titres of antinuclear antibody positivity with normal nailfold capillaroscopy have been observed in disease-discordant twins of scleroderma patients. The more usual scenario is the co-occurrence of both autoantibody positivity and abnormal nailfold capillaroscopy at initial clinical presentation. Assuming this patient's findings truly reflect the prediagnostic disease phase in other individuals, and that both autoantibody abnormalities and nailfold capillaroscopy abnormalities evolve at comparable rates, it suggests that serological changes predate vessel wall abnormalities – that is, the evolution is from within the vessel outwards, rather than vice versa.

Temporal classification of 'prescleroderma' is important because it assists in the understanding and definition of 'scleroderma onset', currently a clinical diagnosis. If prescleroderma inexorably leads to clinical disease, and if early intervention potentially minimizes clinical complications, then a classification of the temporal pattern of prediagnostic scleroderma, such as is now proposed, may serve this end.

References


Atypical clinical presentations of the A3243G mutation, usually associated with MELAS

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Key words
MELAS syndrome, mitochondrial diseases, mitochondrial DNA, rhabdomyolysis, retinitis pigmentosa.

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Abstract
Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is a clinical syndrome associated with mitochondrial abnormalities. In approximately 80% of patients, the syndrome is associated with the A3243G mutation. However, it has been realized that the A3243G mutation is not uncommon in the general population and is found in many patients with clinical presentations other than MELAS. We present four patients who presented with rhabdomyolysis, muscle fatigue, external ophthalmoplegia and myoclonic jerks respectively. These patients were all found to have the A3243G mutation on muscle biopsy. These patients illustrate the variety of presentations associated with A3243G mutation.

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199
The syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) comprises seizures, encephalopathy and stroke-like episodes.\(^1\) Other features include short stature, deafness, cognitive impairment, exercise intolerance, migraines, depression, cardiomyopathy, cardiac conduction defects and diabetes mellitus.\(^2\)

MELAS is frequently associated with a point mutation of the mitochondrial chromosome in the tRNA\(^{Leu(UUR)}\) gene (A3243G).\(^3,4\) Estimations of the prevalence of the A3243G mutation vary widely from 0.95 to 236:100 000\(^5-7\) depending on the methods used, indicating that individuals with the A3243G mutation can be relatively lacking in symptoms.

We have encountered four patients who did not have the typical MELAS syndrome but in whom the A3243G mutation was found using direct PCR amplification of DNA from a muscle sample with subsequent digestion with the diagnostic enzyme ApaI. Using restriction fragment analysis with agarose gel electrophoresis and ethidium bromide staining the degree of heteroplasmy could be estimated.

### Patients

#### Patients 1 and 2

A 51-year-old man presented with a 20-year history of recurrent episodes of rhabdomyolysis. The episodes occurred every 3–5 years, after minimal trauma or dehydration. Creatine kinase levels reached 63 500 U/L (normal <200 U/L), requiring admission to an intensive care unit and short-term haemodialysis for acute renal failure. His serum lactate fluctuated between 1.9 mmol/L and 5.7 mmol/L (<2 mmol/L); however, no acidosis was found on blood gas analysis. In between these episodes he complained of mildly reduced exercise tolerance. Physical examination was normal. A magnetic resonance imaging (MRI) brain showed small vessel ischaemic changes.

A muscle biopsy showed frequent ragged red fibres (RRF) on Gomori Trichrome staining. Mitochondrial gene analysis showed an A3243G mutation load of 40%.

Interestingly, his brother (patient 2), who had poor exercise tolerance, muscle aching since childhood and mental and physical fatigue, and had independently been diagnosed with ‘chronic fatigue syndrome’ also had the A3243G with a mutation load of 10% on muscle biopsy, but no RRF.

#### Patient 3

A 65-year-old man had myoclonic jerks and recurrent generalized seizures since 2006. He had insulin dependent diabetes since age 32; progressive deafness; longstanding, progressive ataxia; progressive short-term memory loss for a number of years; peripheral neuropathy; renal tubular acidosis type IV and ischaemic heart disease. His mother suffered from diabetes and his maternal grandmother, two brothers and one sister had hearing loss. Two of these siblings had diabetes, and one had peripheral neuropathy.

Neurological examination showed normal tone and power but dysarthria, intention tremor, truncal and gait ataxia, jerky ocular pursuit movements, absent ankle jerks, impaired sensation distally for vibration and proprioception and cognitive impairment (Mini-mental State Examination score of 15).

An MRI brain showed cerebral and cerebellar atrophy and minor ischaemic white matter disease. An electroencephalogram was normal. Serum lactate was 3.3 mmol/L and serum pyruvate was 110 μmol/L (<90 μmol/L).

A muscle biopsy showed frequent RRF on histology. Mitochondrial gene analysis showed the A3243G mutation with a mutation load of 5%.

#### Patient 4

A 70-year-old woman had retinitis pigmentosa, with onset of visual problems at age 30 progressing to severe visual impairment. She also had severe bilateral deafness since age 30. She had widespread muscle discomfort in her legs, neck and arms with cramping in feet, poor exercise tolerance and migraine-like headaches.

One of her two brothers suffered from joint pain and hearing loss and her sister from joint pain and retinitis pigmentosa. Both her parents lived to their ninth decade and died of unrelated causes. Her three children were asymptomatic.

Neurological examination showed full power including normal extraocular muscles. She had bilateral hearing aids. The rest of the examination was normal.

Her serum lactate was 1.4 mmol/L. On muscle histology, no RRF were found; however, electron microscopy showed abnormal mitochondrial inclusions. The A3243G mutation load was 20%.

### Discussion

We present four patients whose predominant clinical symptoms were rhabdomyolysis, muscle fatigue, myoclonic jerking and retinitis pigmentosa respectively (Table 1). They were identified as carrying the A3243G mutation.
None of these patients had stroke-like symptoms, which are a hallmark of MELAS. This highlights the variety of possible clinical presentations of patients with this mutation.

Patients 1 and 2 had symptoms mainly involving muscle. Patient 1 was suffering from recurrent episodes of rhabdomyolysis occurring with minimal provocation, with mild exercise intolerance as his only other complaint. Some of these episodes required short-term haemodialysis. A muscle biopsy, performed to exclude metabolic disorders, led to the diagnosis of a mitochondrial disorder. Several other patients with severe episodes of rhabdomyolysis have been described;8–11 however, most of these patients had other manifestations of mitochondrial disease and associated severe lactic acidosis.

Patient 2 had only very mild symptoms of reduced exercise tolerance. Muscle biopsy showed the A3243G mutation with a mutation load of 10%, but no RRF. It is unclear whether this abnormality contributes to his clinical problem of fatigue.

Patients 3 and 4 showed a wide range of involved systems, including retinal, inner ear, peripheral and central nervous system and endocrine disorders combined with a positive family history. In patient 3, myoclonic epilepsy with ragged red fibres was suspected. Patient 4 had retinitis pigmentosa in addition to bilateral severe hearing loss and muscle pain. A mitochondrial disorder was suspected in both patients, but MELAS was not considered prior to biopsy.

Mitochondrial mutations are thought to be not uncommon in oocytes,12 and expression of the disease in later life could vary with the level of heteroplasmy in different tissues. It is thought that for many mitochondrial diseases a certain threshold of percentage of diseased mitochondria needs to be reached within a tissue to cause end-organ dysfunction.13 However, even very low levels of the A3243G mutation can cause mitochondrial dysfunction in vivo.14–16

The percentage of mitochondria with the A3243G mutation varies widely between tissue samples.17,18 In addition, the percentage of mutated mitochondria can change in tissues over time, especially if there is a high turnover of cells.19,20 In tissues like brain and muscle with a low number of mitoses, mutations can persist and have a higher likelihood to cause end-organ dysfunction.3 In contrast, the mutation load in blood is significantly lower than in other tissues. Therefore, the use of other tissues (urinary epithelial cells, hair follicles, skin fibroblast) for screening for mitochondrial disorders has been proposed.17

In summary, the clinical presentation of the A3243G mutation can range from oligosymptomatic patients or even asymptomatic carriers, to severely affected individuals with multi-system involvement. Family history is helpful in some patients. It appears likely that a significant number of patients with non-specific symptoms or atypical diseases actually are suffering from undiagnosed mitochondrial disorders.

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5 Chinnery PF, Johnson MA, Wardell TM, Singh-Kler R, Hayes C, Brown DT et al. The epidemiology of pathogenic mitochondrial DNA
Rituximab-induced serum sickness in refractory immune thrombocytopenic purpura

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Key words
serum sickness, immune thrombocytopenic purpura, rituximab.

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Brief Communications

20 Rajasimha HK, Chinnery PF, Samuels DC, Rajasimha HK, Chinnery PF, Samuels DC. Selection against pathogenic mtDNA mutations in a stem cell population leads to the loss of the 3243A→G mutation in blood. Am J Hum Genet 2008; 82: 333–43.

Abstract
Serum sickness may occur in patients treated with chimeric monoclonal antibody. Rituximab, an anti-CD20 chimeric monoclonal antibody, is used with increasing frequency in chronic immune thrombocytopenic purpura (ITP). Rituximab is relatively safe; however, serum sickness is reported in 1–20% of patients, more commonly among those with autoimmune conditions. We describe a case of serum sickness in a patient with ITP and review the literature of rituximab-induced serum sickness.
There is strong evidence that rituximab is effective in the treatment of immune thrombocytopenic purpura (ITP), and has a safety profile of tolerance. Indeed, this chimeric murine-human monoclonal anti-CD20 antibody is effective in 40% of chronic ITP and rituximab is increasingly proposed before splenectomy. Moreover, tolerance for rituximab is generally good, with transient minor side effects that do not necessitate treatment withdrawal in the majority of cases. However, serious delayed side effects, such as serum sickness, have been reported, particularly when rituximab is used in the treatment of autoimmune diseases as compared with haematologic malignancies. We report a new case of serum sickness after rituximab therapy in ITP.

A 31-year-old woman at 17-week gestation was referred for severe isolated thrombocytopenia (platelet count, 4 × 10^9/L). The medical history was significant for an IgA nephropathy diagnosed 2 years earlier. The clinical examination revealed extensive purpura, bilateral epistaxis and bleeding gums. One month earlier, the platelet count was 300 × 10^9/L. The bone marrow examination showed numerous megakaryocytes and there was no basis for a secondary cause of ITP. As the bleeding score was >8, she was treated with oral prednisone (1 mg/kg a day) and i.v. immunoglobulin (Sandoglobulin, Sandoz, Rueil Malmaison, France (1 g/kg/day)) with a good response (platelet count 2 days after treatment, 150 × 10^9/L).

However, while on oral corticosteroid therapy, the platelet count decreased to <5 × 10^9/L 10 days later, and the severe haemorrhagic syndrome relapsed, leading to a perfusion of i.v. immunoglobulin (1 g/kg/day) without effect. Because of uncontrolled bleeding and anaemia, fractioned platelet pools were added three times a day with prednisone (10 mg/day) and anti-D immunoglobulin (Rhophylac, LFB Biomédicaments, Courtaboeuf, France (75 µg/kg/day)) was administrated. This treatment led to haemolysis, requiring blood transfusion without an effect on the platelet count. Despite the ongoing pregnancy, 10 days after anti-D injection, rituximab was infused at 375 mg/m² weekly with premedication consisting of 1000 mg of paracetamol, 40 mg of prednisolone and 5 mg of dexamethasone maléate.

Thirteen days after the first injection of rituximab, she developed fever, severe diffuse arthralgias, including the temporomandibular joints, an urticarial macular rash, palmar erythema and palpable purpura. Blood tests revealed activation of the classical complement pathway (CH50 < 20% (60–120%), C4 < 0.06 g/L (0.1–0.4), C3, 0.83 g/L (0.8–1.4)), circulating plasmocytosis (2%), inflammatory syndrome (C-reactive protein (CRP), 120 mg/L) and impaired renal function (creatinine, increased from 80 to 120 µmol/L) with mild proteinuria. Testing for Epstein–Barr virus, cytomegalovirus, parvovirus B19 and rheumatoid factor was negative. She received a blood transfusion because of worsening anaemia and was treated with 120 mg of methylprednisolone for 1 day followed by a 7-day oral corticosteroid therapy taper. The clinical symptoms resolved overnight, and the biological abnormalities, including CH50, and C3 and C4 levels, totally normalized after 4 days; the platelet count remained <5 × 10^9/L. A new course of i.v. immunoglobulin (0.4 g/kg/day × 5 days) was administrated, which resulted in an increase in the platelet count to 110 × 10^9/L.

Discussion

Serum sickness is the prototypic example of the Gell & Coombs ‘type III’ or immune complex (IC) hypersensitivity disease, which requires the presence of an antigen, coincident with antibodies directed against the antigen, leading to the formation of the IC. The tissue deposition of the IC and activation of the complement cascade trigger an inflammatory response responsible for the clinical and biological symptoms, as illustrated in our observation, that is, occurrence between 1 and 2 weeks after the first exposure to the responsible agent, clinical manifestations, including fever, urticarial macular rash, palpable purpura, arthralgias (temporomandibular joints), biological abnormalities with an increased CRP level, decreased C3, C4 and CH50 complement levels, circulating plasmocytosis, impaired renal function and rapid resolution after corticosteroid therapy.

The current case is the 32th case of serum sickness reported following rituximab therapy (Table 1). In the case herein, IgG antibodies directed to the murine Fab’ fragments of rituximab were not available (human anti-chimeric antibody (HACA)). However, the diagnostic value of HACA for serum sickness remains unclear. Indeed, patients who develop HACA do not always present with serum sickness in systemic lupus. Nevertheless, patients in these studies also received cyclophosphamide, methotrexate or corticosteroids, which may account for the lack of these events. Moreover, in patients diagnosed with serum sickness, HACA is not always found, which can be explained because an excessive amount of antigen (i.e. rituximab) could consume HACA completely.

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Conflict of interest: None.
Serum sickness is more frequent in autoimmune diseases, particularly in Sjögren’s syndrome, than in lymphoproliferative disorders in which patients are usually treated with polychemotherapy. It is also possible that some factors related to autoimmune disorders, such as reduced clearance of ICs, increased production of autoantibodies, hypergammaglobulinaemia and rheumatoid factor, promote the development of serum sickness. In our observation, the delay seems too long to suggest that anti-D immunoglobulin could have induced serum sickness. However, by saturating the mononuclear phagocyte system in combination with impaired IgA-IC clearance observed in IgA nephropathy, anti-D could have promoted the apparition of serum sickness after rituximab therapy.

As the role of this monoclonal antibody gradually expands, the possibility of serum sickness occurrence should be appreciated by clinicians, particularly when used as a single drug for treatment of autoimmune diseases.

Table 1: Case reports of serum sickness after rituximab therapy

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Cases</th>
<th>Condition</th>
<th>HACA</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Arcy et al., 2001</td>
<td>1</td>
<td>Autoimmune polyneuropathy</td>
<td>Positive</td>
</tr>
<tr>
<td>Herishanu, 2002</td>
<td>1</td>
<td>ITP</td>
<td>NA</td>
</tr>
<tr>
<td>Hellerstedt et al., 2003</td>
<td>1</td>
<td>SLE with ITP</td>
<td>NA</td>
</tr>
<tr>
<td>Catuogno et al., 2004</td>
<td>3/24</td>
<td>Paediatric chronic ITP</td>
<td>NA</td>
</tr>
<tr>
<td>Meng et al., 2005</td>
<td>3/15</td>
<td>SS</td>
<td>Positive</td>
</tr>
<tr>
<td>Bennett et al., 2006</td>
<td>2/36</td>
<td>Paediatric chronic ITP</td>
<td>NA</td>
</tr>
<tr>
<td>Portlock et al., 2006</td>
<td>2/19†</td>
<td>Indolent lymphoma</td>
<td>NA</td>
</tr>
<tr>
<td>Schutgens, 2006</td>
<td>1</td>
<td>SS with MALT lymphoma</td>
<td>NA</td>
</tr>
<tr>
<td>Seror et al., 2007</td>
<td>3</td>
<td>Two SLE</td>
<td>NA</td>
</tr>
<tr>
<td>Todd and Helfgott, 2007</td>
<td>1</td>
<td>One SS with MALT lymphoma</td>
<td>Negative</td>
</tr>
<tr>
<td>Devauchelle-Pensec et al., 2007</td>
<td>1/16</td>
<td>Mantle cell lymphoma</td>
<td>NA</td>
</tr>
<tr>
<td>Finger et al., 2007</td>
<td>2</td>
<td>One SS</td>
<td>NA</td>
</tr>
<tr>
<td>Disperati et al., 2007</td>
<td>1</td>
<td>One undetermined autoimmune disease</td>
<td>NA</td>
</tr>
<tr>
<td>De Monaco and Jacobs, 2007</td>
<td>1/17</td>
<td>Follicular lymphoma</td>
<td>NA</td>
</tr>
<tr>
<td>Dass et al., 2008</td>
<td>1/26</td>
<td>Chronic ITP</td>
<td>NA</td>
</tr>
<tr>
<td>Mehen et al., 2008</td>
<td>1</td>
<td>Mixed connective tissue disease</td>
<td>NA</td>
</tr>
<tr>
<td>Godeau et al., 2008</td>
<td>1/60</td>
<td>ITP</td>
<td>NA</td>
</tr>
<tr>
<td>Goto et al., 2009</td>
<td>1</td>
<td>Paediatric chronic ITP</td>
<td>Positive</td>
</tr>
<tr>
<td>Matsui et al., 2009</td>
<td>2</td>
<td>One Waldenstrom’s macroglobulinaemia</td>
<td>NA</td>
</tr>
</tbody>
</table>

†Unclear whether serum sickness-like symptoms were related to peg-interferon, rituximab or the combination of peg-interferon and rituximab. HACA, human anti-chimeric antibody; HCV, hepatitis C virus; ITP, immune thrombocytopenic purpura; MALT, mucosa-associated lymphoma; NA, not available; SLE, systemic lupus erythematosus; SS, Sjögren’s syndrome.

References
PERSONAL VIEWPOINT

Clinical effectiveness in everyday practice: improving outcomes for all patients through a national acute coronary syndrome data collaborative


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Key words
acute coronary syndrome, healthcare quality, standard, evidence-based practice, quality assurance.

Abstract
The management of acute coronary syndromes (ACS) has an extensive and impressive evidence-base with which to guide clinical practice. Despite this, translation to the clinical environment has proved to be challenging and incomplete and can be attributed to patient, provider and system factors. Causes of suboptimal guideline adherence relate to diverse issues, including patient complexity, barriers in knowledge translation of guideline recommendations and a limited capacity within health services. Addressing these factors may enable more effective guideline implementation. In Australia, the infrastructure for clinical data management is fragmented, uncoordinated and often administratively driven, compromising access to important information, which might improve clinical effectiveness. An integrated approach is required to improve clinical effectiveness in ACS care in Australia. Greater access to information both to assist in clinical decision-making and monitoring outcomes may help direct the focus towards understudied populations and improve performance and clinically relevant outcomes. A peer-led initiative based on common datasets, providing rapid feedback, while developing and disseminating a ‘toolbox’ of proven and sustainable interventions, could improve clinical effectiveness in the Australian management of ACS and provides a rationale for a national ACS registry.

Introduction
Acute coronary syndromes (ACS) are a common, costly and potentially fatal condition in the Australian population. Despite a robust evidence-base, considerable differences remain between recommended and actual care. International organizations have invested in guideline dissemination programmes aimed at translating evidence into practice. Australian efforts to document ACS management have sought to reflect ‘usual care’ and measure clinically relevant outcomes, but lack both the infrastructure and resources to continue as sustainable registries and the detail on system factors that enable institutions to assess effective healthcare delivery. In the contemporary management of ACS, the real challenge lies in the effective and consistent translation of evidence to practice, seeking equitable outcomes for all Australians: the concept of clinical effectiveness. We propose an operational model underpinned by the establishment of a national ACS registry to improve clinical effectiveness delivery in Australia.

Barriers to the translation of evidence-based medicine
Consider Mrs MI presenting to an outer metropolitan hospital with an ST-segment elevation myocardial infarction (STEMI). At 81 years of age, she has a previous history of transient ischaemic attack, hypertension, atrial fibrillation and renal dysfunction with an estimated glomerular filtration rate of 44 mL/min/1.73 m². The attending medical officer is a second-year resident and there is no onsite cardiology service, although a poster representing the Heart Foundation’s protocol for the management of acute myocardial infarction (AMI) is displayed in the emergency room.
Complexity
How well does current evidence inform us of the optimal treatment for Mrs MI?

Patients are becoming increasingly complex to treat as the population ages and patients present with multiple comorbidities. There is a limited evidence-base informing the management of more complex patients, such as those who are elderly and/or have comorbidities such as renal disease, with an ongoing need for anticoagulation. The Global Registry of Acute Coronary Events (GRACE) demonstrated that patients at highest risk of death, as predicted by the GRACE risk score (of comorbidities), were substantially less likely to undergo invasive management. This suggests clinician uncertainty regarding risk: benefit assessment. Recent data from the Acute Coronary Syndromes Prospective Audit (ACACIA) showed that ACS assessment by myocardial risk factors (biomarker rise, electrocardiogram changes, Killip class 2+, haemodynamic compromise) is associated with an increased likelihood of invasive management (3+ vs 0 risk factors: odds ratio (OR) 4.37 (confidence interval (CI): 3.10–6.17, P < 0.001)), while assessment by comorbid risk factors (>75 years, congestive cardiac failure, chronic obstructive pulmonary disease, malignancy, stroke or renal dysfunction) is associated with a lower likelihood of invasive management (4+ vs 0 risk factors: OR 0.09 (CI: 0.06–0.16, P < 0.001)). Understanding the complexity of clinical decision-making and how effectively we balance risk and benefit is crucial, as it is in these higher risk groups that potentially there is most to gain from delivering appropriate treatment options.

Complexity of treatment is also impacted by the under-studied dimension of patient choice. Cost, access, social factors and levels of health literacy can all impact on adherence with guideline recommendations. For Mrs MI who may live alone and come from a non-English-speaking background, the outcomes she values may differ from those evaluated in the ACS evidence-base. Clinicians appreciate that all of these factors impact on outcomes and the care provided. Registry data could also include outcomes which reflect these factors.

Knowledge translation
How prepared is a non-expert workforce to make appropriate decisions and deliver timely evidence-based care for a complex patient with AMI?

Clinical guidelines originated from an initiative to assist in the application of randomized clinical trial evidence into everyday practice. Registry data have consistently demonstrated the discrepancies between recommended and actual treatment and highlight variability between health services in guideline adherence. The Heart Protection Partnership showed that patients treated at centres without interventional facilities were less likely to receive guideline-based medical therapies and referral for coronary angiography than patients treated at centres with interventional facilities (20.1% vs 66.4%; P < 0.001). Furthermore, decision support systems measuring performance and delivering feedback are not commonly available in the clinical environment. Increasing the capability for rapid, risk-based decision-making at the bedside is resource-intensive as it may require electronic systems to be immediately available to the clinician at the point of care. Creative solutions within Australia’s geographic context are urgently needed.

System and process of care factors
Do our hospital environments support the delivery of evidence-based care?

System and process of care factors are characteristics of a health service which may facilitate the delivery of best practice care. For Mrs MI, the lack of a protocol-based system for the delivery of emergent reperfusion therapy reduces the potential for the junior doctor to assess quickly, provide immediate treatment and organize possible transfer to a hospital with interventional facilities. Why do some hospitals perform better in the delivery of ACS care? Some hospitals have systems and processes of care that may assist clinicians to deliver optimal treatment. Examples include guideline-based activation systems for STEMI patients needing timely treatment, quality improvement (QI) tools (management algorithms and discharge checklists), electronic systems, departmental clinical advocates, QI personnel and adequate staffing levels. While QI programmes in the USA have used such clinical care tools as part of their improvement interventions and have shown associations with improved performance outcomes, data on the prevalence of tool use are limited. The Guidelines Applied in Practice pilot showed tool use was documented on the chart in only a quarter of patients.

A way forward
Improving clinical effectiveness in Australian ACS care will require an integrated approach which: (i) builds common and comprehensive local level data across Australia in order to measure treatment and outcomes, (ii) provides capacity to evaluate change in patient and system level care and (iii) is managed under an appropriate governance system which protects stakeholders, while maintaining accountability. Developing electronic data systems
for everyday clinical practice will facilitate knowledge
translation. Developing a ‘toolbox’ of sustainable inter-
ventions to share between health services can build the
capacity of acute care services. All of this must be managed
within a governance structure that monitors accountabil-
ity and respects privacy. This ‘conceptual triad’ of clinical
effectiveness lends itself to a formalized structure.

A central organization

Undertaking clinical effectiveness is both resource and
data intensive. Through a central organization incorpo-
rating a national ACS registry, health services providing
ACS care may gradually build the capacity to collect and
benchmark outcomes, while in turn drawing upon a
common data analysis and reporting facility, located
within a central professional or academic group. Contri-
bution would be voluntary, although it is expected that
benefits to patient care and outcomes to the health
system would drive interest (Table 1).

The central organization would rely upon health ser-
VICES collecting continuous, standardized data on routine
care, performance and outcome, with opportunities for
participation in collaborative research projects. Data
would be submitted to the central organization, where it
would be monitored, analysed and returned to the health
service. Regional project managers would guide and
educate the health service through the various stages and
assist implementation of sustainable interventions that
translate evidence into practice. A governance committee
made up of clinical experts, funders and other consumers
would guide analyses directed at informing system
changes, setting research directions and developing
relationships with the government to advance funding
priorities.

The pivotal feature of the central organization would
be to develop a rapid data monitoring and feedback
system, reporting against key performance indicators.
Evidence shows that this enables improved systems of
care and can be used to inform quality processes.18 It is
thought that by developing an organizational structure of
regional managers and an expert governance team to
support local health services, this will increase the sus-
tainability potential of a national ACS registry. Further,
the cost-effectiveness of a national registry could be
ensured by the benefits of widespread improvement in
clinical care. Studies have demonstrated that by improv-
ing the application of current evidence-based therapies,
greater mortality and morbidity gains can be achieved
than by the development of new therapy innovations.21

How could this model improve outcomes for Mrs MI?

Complexity

Through the data monitoring and feedback cycle, the
junior doctor (and clinicians treating other patients)
would receive outcomes data adjusted for comorbidities,
which would assist in the assessment of Mrs MI’s risk:
benefit options. The central organization could also form
a network for the conduct of research studying the effec-
tiveness of current and emerging therapies in patients
with multiple comorbidities, thus helping to establish

Table 1  Benefits of a national acute coronary syndrome registry

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Design</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Focus on patient choice, health literacy, cost, access and treatment</td>
<td>Improve service availability, quality and outcomes.</td>
</tr>
<tr>
<td></td>
<td>adherence</td>
<td></td>
</tr>
<tr>
<td>Clinicians</td>
<td>Central data group provides regular data feedback. Central group builds</td>
<td>Can assist hospitals to identify problem areas, can then</td>
</tr>
<tr>
<td></td>
<td>a ‘toolbox’ of sustainable improvements from experiences of local</td>
<td>implement improvements which may improve</td>
</tr>
<tr>
<td></td>
<td>participants</td>
<td>performance and clinical outcomes.</td>
</tr>
<tr>
<td>Clinicians, health service providers</td>
<td>Use a prospective, eHealth decision support system at the point of care. Submit data at regular intervals to central data organization.</td>
<td>Network supports change and shares improvements.</td>
</tr>
<tr>
<td>Researchers, clinicians</td>
<td>Unique identifier data linkage with administrative/ procedural datasets. Focus research on populations excluded from RCTs.</td>
<td>Provides mechanism for continuous data collection which can be submitted to central data organization.</td>
</tr>
<tr>
<td>Professional and non-government organizations, health providers, clinicians</td>
<td>Governance group who are clinical, policy and data experts oversee and guide data analyses.</td>
<td>Develops a national dataset of performance and outcomes allowing benchmarking and identification of priorities.</td>
</tr>
</tbody>
</table>

eHealth, electronic health; RCT, randomized clinical trial.

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evidence-based treatment options in such populations. With research participation being part of the organization, Mrs MI may consent to participate in research that studies the effectiveness of a risk factor modification programme, also creating the potential for assisting Mrs MI’s understanding of the concept of self-care and lifestyle modifications.

**Knowledge translation**

Like many initiatives, the national registry that develops from the central organization may be implemented through a web-based clinical interface with real-time decision support. This could be used by the junior doctor to assess Mrs MI’s risk and guide the delivery of evidence-based treatment options. Such decision support offers the opportunity for knowledge resources to be tightly integrated within the daily workflow of clinical care.

**System and process of care factors**

Through comparative data and an understanding of local systems of care, factors impeding or facilitating the delivery of current evidence within health services can be identified. This can inform the need for health service level investment in proven strategies that create clinical environments that improve the delivery of care. Through acquired data and experience, health providers may build a collection of sustainable evidence-based interventions, examples of which could be patient education materials to help Mrs MI to understand her heart attack, or a discharge checklist for medical staff linked to the clinical interface of the database and recommending guideline medications at discharge.

**Conclusion**

Successfully applying evidence-based care to practice is challenging and to this time, has been incomplete. Causes relate to issues of complexity, knowledge translation and health service system and process of care factors. An integrated system is required to improve clinical effectiveness in Australian ACS care. A patient-centred approach may direct the focus towards improving performance and clinical outcome. A peer-led initiative that encompasses standardized data infrastructure, provides rapid feedback, develops a ‘toolbox’ of sustainable interventions and is overseen by experts and relevant stakeholders, could be achieved by the establishment of a collaborative national ACS registry.

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IMAGES IN MEDICINE

Beware the glass-eyed patient with liver enlargement

A 57-year-old man presented with a 2-week history of progressive malaise, confusion, leg oedema and abdominal distension. Physical examination revealed profound jaundice sparing his right eye (Fig. 1a), an enlarged liver, ascites and marked peripheral oedema. He had marked leucocytosis, thrombocytopenia, elevated liver enzymes, hypoalbuminaemia, a prolonged international normalized ratio and an ammonia level of 90 µmol/L (normal < 50). Abdominal sonography and subsequent computed tomography showed no evidence of biliary obstruction, but there were multiple hepatic lesions consistent with metastases (Fig. 1b). Ascitic leukocyte count was 60/µL.

He was treated with antibiotics and lactulose for suspected ascending cholangitis and hepatic encephalopathy. Over the following days he developed fulminant hepatic failure. Two years previously, he had undergone right eye enucleation for a choroidal melanoma and had a right ocular prosthesis. Choroidal melanoma, the most common intraocular malignancy in North America, most often metastasizes to the liver. A ‘glass eye-enlarged liver’ syndrome was characterized by de Lajarte et al. in 1993.1

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Figure 1 (a) Unicocular (left) scleral icterus. (b) Computerized tomography scan of the liver showing multiple metastases.
A 42-year-old man who was being evaluated for bilateral oedema of the lower limbs was referred with complaints of severe left-sided abdominal pain radiating to the left testis. A day after the onset of pain, the patient noticed swelling and redness of his scrotum more so on the left side. Urinalysis revealed 4+ protein and numerous fresh red blood cells. Twenty-four-hour urine protein excretion was 8.4 g. Considering the possibility of renal vein thrombosis, an urgent computerized tomographic (CT) scan of the abdomen and pelvis with a CT renal angiogram was performed. This confirmed extensive left renal vein thrombosis. The left kidney was enlarged with perinephric fat stranding. There was also evidence of a left varicocele. The patient was transferred to a tertiary hospital where he underwent catheter-directed renal vein thrombolysis. A kidney biopsy performed subsequently confirmed membranous nephropathy.

Renal vein thrombosis is a well-known complication of nephrotic syndrome. The prevalence of renal vein thrombosis is highest in membranous nephropathy, although it has been well documented in other causes of nephrotic syndrome. The diagnosis of renal vein thrombosis can be made by renal vein angiography or through less invasive measures, such as helical CT angiography, magnetic resonance renal angiography or Doppler ultrasonography of renal veins. Treatment of renal vein thrombosis involves full anticoagulation using low molecular weight or unfractionated heparin. In addition, there is also a role for fibrinolytic agents and surgical thrombectomy especially if the patient presents early in order to prevent renal infarction.

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LETTERS TO THE EDITOR

Clinical-scientific notes

Phaeochromocytoma, neurofibromatosis and gastrointestinal stromal tumour: just a random event?

A 39-year-old man with neurofibromatosis type 1 (NF-1) and untreated hypertension presented with right flank pain following a fall. He suffered from significant episodes of anxiety, sweating, palpitations and headaches attributed to alcohol abuse. His mother has NF-1 and phaeochromocytoma.

Investigation of his flank pain led to an abdominal computed tomography (CT) scan, which revealed a right adrenal lesion, measuring 6.3 x 5.5 x 4.5 cm. The left adrenal gland appeared normal. However, a second well-defined mass was identified in the mesentery, adjacent to the small bowel, measuring 2.9 x 3.2 x 3.5 cm. His serum and 24-h urine catecholamines were markedly elevated (Table 1).

Following α- and β-adrenergic blockade, a laparoscopic right adrenalectomy was performed, together with a mini-laparotomy for small bowel exploration. A pedunculated lesion was excised from the small bowel. Histopathology of the adrenal gland tumour was consistent with phaeochromocytoma with no malignant features. The intestinal lesion was a gastrointestinal stromal tumour (GIST), with features suggesting malignant potential. Molecular analysis of exons 9, 11, 13 and 17 of tyrosine kinase receptor, KIT gene, as well as exons 12 and 18 of platelet-derived growth factor receptor-alpha (PDGFRA) gene revealed no somatic mutations.

Postoperatively, his biochemistry normalized (Table 1). He was commenced on adjuvant imatinib mesylate therapy. Longitudinal care includes early detection and symptomatic treatment of NF-1-associated complications.

Phaeochromocytomas have been identified in 0.1–5.7% of patients with NF-1, with incidence rising to 50% in patients with NF-1 plus hypertension.1 NF-1 is an autosomal dominant disorder with variable penetrance, caused by mutations of the NF1 gene, which encodes neurofibromin, a negative regulator of RAS activation, leading to abnormal tumour suppression. Hence, patients with NF-1 can present with a variety of neoplasms, mainly involving tissues of neuroectodermal or mesenchymal origin, including GISTs.2,3 GISTs comprise 1–3% of all malignant gastrointestinal tumours, are often asymptomatic and have been reported in up to 25% of NF-1 patients. A recent analysis of 3000 GIST cases suggests that NF-1 patients have at least a 45-fold higher risk of GIST than the general population.4,5 Most sporadic GISTs contain mutations in the KIT gene (exons 9, 11, 13,

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Catecholamine and metanephrine levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient level (preoperative)</td>
<td>Patient level (postoperative)†</td>
</tr>
<tr>
<td><strong>Urine biogenic amines</strong></td>
<td></td>
</tr>
<tr>
<td>Noradrenaline (nmol/day)</td>
<td>2044</td>
</tr>
<tr>
<td>Adrenaline (nmol/day)</td>
<td>2610</td>
</tr>
<tr>
<td>Normetanephrine (µmol/day)</td>
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</tr>
<tr>
<td>Metanephrine (µmol/day)</td>
<td>32.9</td>
</tr>
<tr>
<td><strong>Plasma metanephrines</strong></td>
<td></td>
</tr>
<tr>
<td>Normetanephrine (nmol/l)</td>
<td>4.11</td>
</tr>
<tr>
<td>Metanephrine (nmol/l)</td>
<td>6.45</td>
</tr>
</tbody>
</table>

†6 month post-operative level.
17) and in the PDGFRA gene (exons 12 and 18). In contrast, NF-1-associated GISTs usually do not contain these mutations and subsequently, tend to be poorly responsive to imatinib.6

To date, only eight cases of simultaneous occurrence of phaeochromocytoma, NF-1 and GIST have been reported. In all cases, GISTs were incidental intraoperatively. As GISTs are difficult to detect preoperatively, it is highly likely they are under-reported. The increased risk of both phaeochromocytoma and GISTs in NF-1 are well documented, hence raising the possibility that the coexistence of the three may be more than just a random event. If awareness is increased, more cases may come to light.

References

Reversal of cardiomyopathy with ivabradine

A 22-year-old woman presented with a 2-month history of increasing exertional dyspnoea and a 3-day history of fever and a productive cough. There was no other significant personal history and no family history of cardiac disease. On examination she was tachycardic with heart rate varying between 150 and 200 b.p.m., temperature 37.5°C, blood pressure 108/60 mmHg and respiratory rate 30 bpm. Cardiorespiratory examination revealed elevation of the jugular venous pressure (JVP), cardiomegaly with a displaced apex beat, S3 gallop and signs of left basal consolidation.

Initial blood tests revealed an undetectable troponin level, normal white blood cell count and mildly elevated C-reactive protein. Computed tomography pulmonary angiography excluded pulmonary embolism but demonstrated cardiomegaly and left lower lobe consolidation. Electrocardiogram showed a narrow complex tachycardia at a rate of ~150/min without discernible P waves. The tachycardia did not terminate with intravenous adenosine or metoprolol, nor with an amiodarone infusion, although transient rate slowing was noted. The interim diagnosis was decompensated heart failure most likely precipitated by left lower lobe pneumonia. She was transferred to our hospital for ongoing care.

An echocardiogram showed mild left ventricular (LV) dilatation and severe global dysfunction with an LV ejection fraction of 10%. Thyroid function, 24-h urinary catecholamines, autoimmune screen and viral serology were all unremarkable. Endomyocardial biopsy showed mild myopathic changes only.

She was commenced on heart failure therapy leading to improvement in heart failure; however, her tachycardia persisted. A cardiac electrophysiology study demonstrated the tachycardia to be originating in the region of the sinus node. Entrainment mapping was performed from several sites in the right atrium. Postspacing interval
was always >50 ms greater than the tachycardia cycle length. Pacing was followed by slowing of the rate and then gradual increase to the tachycardia rate. No termination of the arrhythmia or induction of other arrhythmias was seen with extrastimulus testing. The patient was given a diagnosis of tachycardia-induced cardiomyopathy due to inappropriate sinus tachycardia.

Her metoprolol dose was progressively up-titrated and she was discharged home on metoprolol succinate (Toprol XL, AstraZeneca, London, UK) 190 mg/day and digoxin 125 µg/day. At outpatient review some improvement in LV function was noted (ejection fraction 20–25%); however, she was noted to have persistent sinus tachycardia with rates of up to 120/min despite ongoing up-titration of Toprol to 380 mg/day.

She represented 9 months later with worsening heart failure. The tachycardia was more pronounced with rates around 140/min at rest. She was commenced on ivabradine 5 mg BD and metoprolol dose was halved. A marked reduction in heart rates followed (Fig. 1) with increased exercise tolerance and improved echocardiographic parameters.

A significant component of this patient’s cardiomyopathy appeared to be related to inappropriate sinus tachycardia. The use of ivabradine, a selective inhibitor of If sodium channel currents within the sino-atrial node, led to a dramatic clinical improvement and substantial increase in LV ejection fraction. A dramatic response to ivabradine in a similar case was recently reported by Winum and colleagues.1 Specific heart rate lowering with ivabradine reduces myocardial oxygen demand, simultaneously improving oxygen supply and LV function.2 Ivabradine has no negative inotropic or lusitropic effects, preserving ventricular contractility, and does not change any major electrophysiological parameters unrelated to heart rate. We propose that in patients with tachycardia-induced cardiomyopathy, resistant to beta-blockers, ivabradine may be a worthwhile additional therapy.

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Royal Australasian College of Physicians’ advanced training outside of Australia and New Zealand: trainees’ and supervisors’ perspectives

This year marks the fifth anniversary since a hospital outside of Australia or New Zealand received ‘site’ accreditation for advanced physician training with the Royal Australasian College of Physicians (RACP). Since then, the infectious diseases division at the National University Hospital (NUH), Singapore has supervised eight advanced trainees and was re-accredited in 2009. More recently, the College has accredited four additional overseas hospitals, including two others in Singapore (for infectious diseases) and one each in the UK and Canada (for haematology and paediatric gastroenterology respectively). We reflect on the lessons from NUH.

In 2005, the infectious diseases division at NUH applied for RACP site accreditation which required the meeting of certain criteria and a signed declaration by a resident Fellow of the RACP qualified supervisor. Subsequent, more definitive accreditation required a site visit by the Specialist Advisory Committee to assess the ability of the site to provide the range of experience and infrastructure needed for clinical training. Factors such as the number and range of patients seen, adequacy of supervision, research and educational opportunities and learning infrastructure (e.g. library facilities) were assessed and deemed adequate, and so the site was given accreditation for future RACP advanced trainees also to undergo training there. The site will be reviewed on a 3 to 5 yearly basis.

Compared to an arrangement whereby trainees apply for ad hoc accreditation of training at overseas sites, site accreditation offers significant benefits for both trainees and supervisors. It has enabled NUH to develop a structured training programme and a greater degree of forward planning with regard to trainee selection and research projects. Since 2005, NUH has received an increasing number of applicants for its training position, some of whom have extended their stay in Singapore.

Practising medicine in a foreign country provides a breadth of opportunities. This is particularly so for infectious diseases in Asia where the local epidemiology of micro-organisms, resistance profiles and disease processes differs significantly from other regions of the world.\(^1\) In Singapore, the annual numbers of dengue fever cases are over 10 000. Late presentations of HIV infection, frequent extra pulmonary tuberculosis and infections of the tropics, including melioidosis and typhoid, offer unique training experiences. Antimicrobial prescribing practices are necessarily very different in an environment of endemic multi-resistant (particularly Gram-negative) organisms. Offsetting the complex casemix and busy workload at NUH (average eight consultations per day), protected time for teaching and research is ensured and attendance at conferences and other training opportunities is supported. Past trainees boast a list of publications, course attendances and oral and poster presentations at international meetings. Aided by strong links with the National University of Singapore, trainees are also heavily involved in both under- and postgraduate teaching as well as undergraduate examinations. Juggling a busy clinical load, teaching and research in a foreign setting demands that the trainee be able to work independently, be proactive and capable of multitasking.

For registrars contemplating overseas training, planning needs to commence early. In Singapore, obtaining contracts, medical registration and an employment pass takes approximately 6 months. Approval of training is the same as for those working in Australia or New Zealand.

The 5-year NUH experience has created a possible template for the extension of RACP advanced training at an accredited site outside of our traditional geographic boundaries. Options for a more diverse training and life experience during advanced training outside of Australia or New Zealand are available and can only serve the global community of future physicians positively.

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